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CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Hypertensive Crises*

Challenges and Management

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Hypertension affects > 65 million people in the United States and is one of the leading causes of death. One to two percent of patients with hypertension have acute elevations of BP that require urgent medical treatment. Depending on the degree of BP elevation and presence of end-organ damage, severe hypertension can be defined as either a hypertensive emergency or a hypertensive urgency. A hypertensive emergency is associated with acute end-organ damage and requires immediate treatment with a titratable short-acting IV antihypertensive agent. Severe hypertension without acute end-organ damage is referred to as a *hypertensive urgency* and is usually treated with oral antihypertensive agents. This article reviews definitions, current concepts, common misconceptions, and pitfalls in the diagnosis and management of patients with acutely elevated BP as well as special clinical situations in which BP must be controlled.

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

Abbreviations: ACE = angiotensin-converting enzyme; APH = acute postoperative hypertension; DBP = diastolic BP; FDA = Food and Drug Administration; JNC = Joint National Committee; MAP = mean arterial pressure; SBP = systolic BP

Hypertension is one of the most common chronic medical conditions in the United States, affecting close to 30% of the population > 20 years old.[1] While chronic hypertension is an established risk factor for cardiovascular, cerebrovascular, and renal disease, acute elevations in BP can result in acute end-organ damage with significant morbidity. Hypertensive emergencies and hypertensive urgencies (see definitions below) are commonly encountered by a wide variety of clinicians. Prompt recognition, evaluation, and appropriate treatment of these conditions are crucial to prevent permanent end-organ damage. This article reviews our current understanding of hypertensive crises, the common misconceptions and pitfalls in its diagnosis and management, as well as pharmacotherapy and special situations that clinicians may encounter.

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Definitions

The classification and approach to hypertension undergoes periodic review by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, with the most recent report (JNC 7) having been released in 2003 (Table 1).[2] Although not specifically addressed in the JNC 7 report, patients with a systolic BP (SBP) > 179 mm Hg or a diastolic BP (DBP) > 109 mm Hg are usually considered to be having a "hypertensive crisis." The 1993 report[3] of the JNC proposed an operational classification of hypertensive crisis as either "hypertensive emergencies" or "hypertensive urgencies." This classification remains useful today. Severe elevations in BP were classified

Table 1—*JNC 7 BP Categorization

BP Class	SBP, mm Hg	DBP, mm Hg
Normal	< 120	< 80
Prehypertension	121–139	80–89
Stage I	140–159	90–99
Stage II	≥ 160	≥ 100

*From Chobanian et al.[2]

as hypertensive emergencies in the presence of acute end-organ damage, or as hypertensive urgencies in the absence of acute target-organ involvement. Distinguishing hypertensive urgencies from emergencies is important in formulating a therapeutic plan. Patients with hypertensive urgency should have their BP reduced within 24 to 48 h, whereas patients with hypertensive emergency should have their BP lowered immediately, although not to "normal" levels. The term *malignant hypertension* has been used to describe a syndrome characterized by elevated BP accompanied by encephalopathy or acute nephropathy.[4] This term, however, has been removed from National and International Blood Pressure Control guidelines and is best referred to as a *hypertensive emergency*.

Epidemiology

Hypertensive emergencies were first described by Volhard and Fahr[5] in 1914, who saw patients with severe hypertension accompanied by signs of vascular injury to the heart, brain, retina, and kidney. This syndrome had a rapidly fatal course, ending in heart attack, renal failure, or stroke. It was not, however, until 1939 when the first large study[6] of the natural history of hypertensive emergencies was published. The results of this seminal article by Keith and colleagues[6] revealed that untreated hypertensive emergencies had a 1-year mortality rate of 79%, with a median survival of 10.5 months. Prior to the introduction of antihypertensive medications, approximately 7% of hypertensive patients had a hypertensive emergency.[7] Currently, it is estimated that 1 to 2% of patients with hypertension will have a hypertensive emergency at some time in their life.[8,9]

In the United States, hypertensive emergencies continue to be quite common, and the epidemiology of this disorder parallels the distribution of essential hypertension, being higher among the elderly and African Americans, with men being affected two times more frequently than women.[10,11] Despite the development of increasingly effective antihypertensive treatments over the past 4 decades, the incidence of hypertensive emergencies has increased.[12]

The vast majority of patients presenting with a hypertensive emergency to an emergency department have a previous diagnosis of hypertension and have been prescribed antihypertensive agents.[10,13] However, in many of these patients BP control prior to presentation was inadequate.[13] The lack of a primary care physician, as well as the failure to adhere to prescribed antihypertensive regimens have been associated with the development of a hypertensive emergency.[14,15] In some studies,[15] > 50% of patients presenting to an emergency department with a hypertensive emergency were not adherent with their antihypertensive medication regimen in the preceding week. In both major metropolitan areas and smaller communities, illicit drug use has been reported[14] to be a major risk factor for the development of hypertensive emergency.

Pathophysiology

Acute severe hypertension can develop *de novo* or can complicate underlying essential or secondary hypertension. The factors leading to the severe and rapid elevation of BP in patients with hypertensive crises are poorly understood. The rapidity of onset suggests a triggering factor superimposed on preexisting hypertension. Hypertensive crisis is thought to be initiated by an abrupt increase in systemic vascular resistance likely related to humoral vasoconstrictors.[16,17] The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased permeability, activation of the coagulation cascade and platelets, and deposition of fibrin. With severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue.[16,17] This process results in ischemia and the release of additional vasoactive mediators generating a vicious cycle of ongoing injury. The renin-angiotensin system is often activated, leading to further vasoconstriction and the production of proinflammatory cytokines such as interleukin-6.[18,19] The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency.

Clinical Presentation

Most patients have persistent BP elevation for years before they manifest a hypertensive emergency. The clinical manifestations of hypertensive emergency are directly related to the particular end-organ dysfunction that has occurred (Table 2).

Table 2—*Clinical Manifestation of Hypertensive Emergencies

Hypertensive encephalopathy
Acute aortic dissection
Acute myocardial infarction
Acute coronary syndrome
Pulmonary edema with respiratory failure
Severe pre-eclampsia, HELLP syndrome, eclampsia
Acute renal failure
Microangiopathic hemolytic anemia
APH

*HELLP = hemolysis, elevated liver enzymes, low platelets.

The signs and symptoms therefore vary from patient to patient. Zampaglione and colleagues[20] reported that the most frequent presenting signs in patients with hypertensive emergencies were chest pain (27%), dyspnea (22%), and neurologic deficits (21%). No particular BP threshold has been associated with the development of a hypertensive emergency. However, organ dysfunction is uncommon with a DBP < 130 mm Hg (except in children and pregnancy).[21] The absolute level of BP may not be as important as the rate of increase. For example, in patients with long-standing hypertension, a SBP of 200 mm Hg or a DBP up to 150 mm Hg may be well tolerated without the development of hypertensive encephalopathy; whereas in children and pregnant women, encephalopathy may develop with a DBP of only 100 mm Hg.[22]

Initial Evaluation

Patients with hypertensive emergency usually present for evaluation as a result of a new symptom complex related to their elevated BP. Patient triage and physician evaluation should proceed expeditiously to prevent ongoing end-organ damage. A focused medical history that includes the use of any prescribed or over-the-counter medications should be obtained. If the patient is known to have hypertension, their hypertensive history, previous control, current antihypertensive medications with dosing, adherence with their medication regimen, and the time from last dose are important facts to acquire prior to initiating treatment. Inquiry into the use of recreational drugs (amphetamines, cocaine, phencyclidine) or monoamine oxidase inhibitors should be made. Confirmation of the BP should be obtained by a physician in both arms using an appropriate-size BP cuff. The appropriate-size cuff is particularly important because the use of a cuff too small for the arm has been shown to artificially elevate BP readings in obese patients.[23,24]

The physical examination should attempt to identify evidence of end-organ damage by assessing pulses in all extremities, auscultating the lungs for evidence of pulmonary edema, the heart for murmurs or gallops, the renal arteries for bruits, and performing a focused neurologic and fundoscopic examination. Headache and altered level of consciousness are the usual manifestations of hypertensive encephalopathy.[25,26] Focal neurologic findings, especially lateralizing signs, are uncommon in hypertensive encephalopathy, being more suggestive of a cerebrovascular accident. Subarachnoid hemorrhage should be considered in patients with a sudden onset of a severe headache. The ocular examination may show evidence of advanced retinopathy with arteriolar changes, exudates, hemorrhages, or papilledema assisting in the identification of hypertensive encephalopathy. Cardiac evaluation should aim to identify angina or myocardial infarction with the focus on clarifying any atypical symptoms such as dyspnea, cough, or fatigue that may be overlooked.[10,27] On the basis of this evaluation, the clinician should be able to distinguish between a hypertensive emergency or an urgency and to formulate the subsequent plan for further diagnostic tests and treatment.

If the clinical picture is consistent with aortic dissection (severe chest pain, unequal pulses, widened mediastinum), a contrast CT scan or MRI of the chest should be obtained promptly to rule out aortic dissection. Although transesophageal echocardiography has excellent sensitivity and specificity for aortic dissection, this study should not be performed until adequate blood control has been achieved. In patients presenting with pulmonary edema, it is important to obtain an echocardiogram to distinguish between diastolic dysfunction, transient systolic dysfunction, or mitral regurgitation.[28] Many patients, particularly the elderly, have a normal ejection fraction, and in such patients heart failure is due to isolated diastolic dysfunction.[28] The management these patients differs from those patients with predominant systolic dysfunction and those with transient mitral regurgitation (Table 3).

Initial Management of BP

The majority of patients in whom severe hypertension (SBP > 160 mm Hg, DBP > 110 mm Hg) is identified on initial evaluation will have no evidence of end-organ damage and thus have a hypertensive urgency. Since no acute end-organ damage is present, these patients may present for evaluation of another complaint, and the elevated BP may represent an acute recognition of chronic hypertension. In these patients, utilizing oral medications to lower the BP gradually over 24 to 48 h is the best approach to management. Rapid reduction of BP may be associated with significant morbidity in hypertensive ur-

Table 3—*Recommended Antihypertensive Agents for Hypertensive Crises*

Conditions	Preferred Antihypertensive Agents
Acute pulmonary edema/systolic dysfunction	Nicardipine, fenoldopam, or nitroprusside in combination with nitroglycerin and a loop diuretic
Acute pulmonary edema/diastolic dysfunction	Esmolol, metoprolol, labetalol, or verapamil in combination with low-dose nitroglycerin and a loop diuretic
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin
Hypertensive encephalopathy	Nicardipine, labetalol, or fenoldopam
Acute aortic dissection	Labetalol or combination of nicardipine and esmolol or combination of nitroprusside with either esmolol or IV metoprolol
Pre-eclampsia, eclampsia	Labetalol or nicardipine
Acute renal failure/microangiopathic anemia	Nicardipine or fenoldopam
Sympathetic crisis/cocaine overdose	Verapamil, diltiazem, or nicardipine in combination with a benzodiazepine
APH	Esmolol, nicardipine, or labetalol
Acute ischemic stroke/intracerebral bleed	Nicardipine, labetalol, or fenoldopam

gency due to a rightward shift in the pressure/flow autoregulatory curve in critical arterial beds (cerebral, coronary, renal).[29] Rapid correction of severely elevated BP below the autoregulatory range of these vascular beds can result in marked reduction in perfusion causing ischemia and infarction. Therefore, although the BP must be reduced in these patients, it must be lowered in a slow and controlled fashion to prevent organ hypoperfusion.

Altered autoregulation also occurs in patients with hypertensive emergency, and since end-organ damage is present already, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury. Therefore, patients with a hypertensive emergency are best managed with a continuous infusion of a short-acting, titratable antihypertensive agent. Due to unpredictable pharmacodynamics, the sublingual and IM route should be avoided. Patients with a hypertensive emergency should be managed in an ICU with close monitoring. For those patients with the most severe clinical manifestations or with the most labile BP, intra-arterial BP monitoring may be prudent. There are a variety of rapid-acting IV agents that are available for use in patients with hypertensive emergency, and the agent of choice depends on which manifestation of end-organ damage is present and the available monitored setting (Table 3). Rapid-acting IV agents should not be used outside of an ICUs monitored setting to prevent precipitous falls of BP that may have significant morbidity or mortality. The immediate goal is to reduce DBP by 10 to 15% or to approximately 110 mm Hg over a period of 30 to 60 min. In patients with aortic dissection, the BP should be reduced rapidly (within 5 to 10 min), targeting a SBP of < 120 mm Hg and mean arterial pressure (MAP) < 80 mm Hg.[30,31] Once there is stable BP control with IV agents and end-organ damage has ceased, oral therapy can be initiated as the IV agents are slowly titrated down. An important consideration prior to initiating IV therapy is to assess the patient's volume status. Due to pressure natriuresis, patients with hypertensive emergencies may be volume depleted, and restoration of intravascular volume with IV saline solution will serve to restore organ perfusion and prevent a precipitous fall in BP when antihypertensive regimens are initiated.

Pharmacologic Agents Used in the Treatment of Hypertensive Emergencies

A number of drugs are available for the management of hypertensive emergency. The agent of choice in any particular situation will depend on the clinical presentation (Table 3). The preferred agents include labetalol, esmolol, nicardipine, and fenoldopam. Phentolamine and trimethaphan camsylate are less commonly used today; however, they may be useful in particular situations such as catecholamine-induced hypertensive crises (*ie*, pheochromocytoma). Sodium nitroprusside may be used in patients with acute pulmonary edema and/or severe left ventricular dysfunction and in patients with aortic dissection.[32] Oral and sublingual nifedipine are potentially dangerous in patients with hypertensive emergencies and are not recommend. Clonidine and angiotensin-converting enzyme (ACE) inhibitors are long acting and poorly titratable; however, these agents may be useful in the management of hypertensive urgencies. ACE inhibitors are contraindicated in pregnancy.[33,34] Clevidipine is a relatively new agent under investigation for the management of postoperative hypertension and hypertensive emergencies.[35] At this time, clevidipine is not available in the United States for use outside of clinical

trials. The recommended IV antihypertensive agents are reviewed briefly below. Dosage and adverse effects of commonly used parenteral antihypertensive medications are listed in Table 4.

Labetalol

Labetalol is a combined selective α_1-adrenergic and nonselective β-adrenergic receptor blocker with an α- to β-blocking ratio of 1:7.[36] Labetalol is metabolized by the liver to form an inactive glucuronide conjugate.[37] The hypotensive effect of labetalol begins within 2 to 5 min after its IV administration, reaching a peak at 5 to 15 min following administration, and lasting for about 2 to 4 h.[37,38] Due to its β-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure β-adrenergic blocking agents that decrease cardiac output, labetalol maintains cardiac output.[39] Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal, and coronary blood flow are maintained.[39–42] This agent has been used in the setting of pregnancy-induced hypertensive crisis because little placental transfer occurs mainly due to the negligible lipid solubility of the drug.[39]

Labetalol may be administered as loading dose of 20 mg, followed by repeated incremental doses of 20 to 80 mg at 10-min intervals until the desired BP 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 is particularly effective. Bolus injections of 1 to 2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided.[43]

Nicardipine

Nicardipine is a second-generation dihydropyridine derivative calcium-channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activity. The onset of action of IV nicardipine is from 5 to 15 min, with a duration of action of 4 to 6 h. IV nicardipine has been shown to reduce both cardiac and cerebral ischemia.[44] The nicardipine dosage is independent of the patient's weight, with an initial infusion rate of 5 mg/h, increasing by 2.5 mg/h every 5 min to a maximum of 15 mg/h until the desired BP reduction is achieved.[21] A useful therapeutic benefit of nicardipine is that the agent has been demonstrated to increase both stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance.[44–48] This property is useful in patients with coronary artery disease and systolic heart failure.

Esmolol

Esmolol is an ultrashort-acting cardioselective, β-adrenergic blocking agent.[49–51] The onset of action of this agent is within 60 s, with a duration of action of 10 to 20 min.[49–51] The metabolism of esmolol is via rapid hydrolysis of ester linkages by RBC esterases and is not dependant on renal or hepatic function. Due to its pharmacokinetic properties, some authors[21] consider it an "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. Esmolol is particularly useful in severe postoperative hypertension.[52–58] Esmolol is a suitable agent in situations in which cardiac output, heart rate, and BP are increased. Typically, the drug

Table 4—*Dosage and Adverse Effects of Commonly Used Parenteral Antihypertensive Medications*

Agents	Dosage	Adverse Effects
Enalaprilat	1.25 mg over 5 min every 4 to 6 h, titrate by 1.25-mg increments at 12- to 24-h intervals to maximum of 5 mg q6h	Variable response, potential hypotension in high renin states, headache, dizziness
Esmolol	500 μg/kg loading dose over 1 min, infusion at 25 to 50 μg/kg/min, increased by 25 μg/kg/min every 10 to 20 min to maximum of 300 μg/kg/min	Nausea, flushing, first-degree heart block, infusion site pain
Fenoldopam	0.1 μg/kg/min initial dose, 0.05 to 0.1 μg/kg/min increments to maximum of 1.6 μg/kg/min	Nausea, headache, flushing
Labetalol	20-mg initial bolus, 20- to 80-mg repeat boluses or start infusion at 2 mg/min with maximum 24-h dose of 300 mg	Hypotension, dizziness, nausea/vomiting, paresthesias, scalp tingling, bronchospasm
Nicardipine	5 mg/h, increase at 2.5 mg/h increments every 5 min to maximum of 15 mg/h	Headache, dizziness, flushing, nausea, edema, tachycardia
Nitroglycerin	5 μg/min, titrated by 5 μg/min every 5 to 10 min to maximum of 60 μg/min	Headache, dizziness, tachyphylaxis
Nitroprusside	0.5 μg/kg/min, increase to maximum of 2 μg/kg/min to avoid toxicity	Thiocyanate and cyanide toxicity, headache, nausea/vomiting, muscle spasm, flushing
Phentolamine	1- to 5-mg boluses, maximum 15-mg dose	Flushing, tachycardia, dizziness, nausea/vomiting

is administered as a 0.5 to 1 mg/kg loading dose over 1 min, followed by an infusion starting at 50 μg/kg/min and increasing up to 300 μg/kg/min as necessary.

Fenoldopam

Fenoldopam is unique among the parenteral BP agents because it mediates peripheral vasodilation by acting on peripheral dopamine-1 receptors. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without participation of cytochrome P-450 enzymes. The onset of action is within 5 min, with the maximal response being achieved by 15 min.[59–61] The duration of action is from 30 to 60 min, with the pressure gradually returning to pretreatment values without rebound once the infusion is stopped.[59–61] No adverse effects have been reported.[59] An initial starting dose of 0.1 μg/kg/min is recommended. Fenoldopam improves creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function.[62–64] The use of fenoldopam as a prophylactic agent to prevent contrast-induced nephropathy has been disappointing.[65,66]

Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload.[67,68] Nitroprusside decreases cerebral blood flow while increasing intracranial pressure, effects that are particularly disadvantageous in patients with hypertensive encephalopathy or following a cerebrovascular accident.[69–72] In patients with coronary artery disease, a significant reduction in regional blood flow (coronary steal) can occur.[73] In a large randomized, placebo-controlled trial,[74] 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%). Nitroprusside is a very potent agent, with an onset of action of seconds, a duration of action of 1 to 2 min, and a plasma half-life of 3 to 4 min.[67] Due to its potency, rapidity of action, and the development of tachyphylaxis, we recommend intraarterial BP monitoring. In addition, sodium nitroprusside requires special handling to prevent its degradation by light. These factors limit the use of this drug.[15]

Nitroprusside contains 44% cyanide by weight.[75] 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.[75] Thiosulfate is required for this reaction.[75,76] 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. Nitroprusside may therefore cause cytotoxicity due to the release of cyanide with interference of cellular respiration.[77,78] Cyanide toxicity has been documented to result in "unexplained cardiac arrest," coma, encephalopathy, convulsions, and irreversible focal neurologic abnormalities.[68,79] 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.[75] 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.[75] Data suggest that nitroprusside infusion rates >4 μg/kg/min, for as little as 2 to 3 h may lead to cyanide levels in the toxic range.[75] The recommended doses of nitroprusside of up to 10 μg/kg/min results in cyanide formation at a far greater rate than human beings can detoxify. Sodium nitroprusside has also been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation.[77,80–82]

Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other IV antihypertensive agents are not available and then only in specific clinical circumstances and in patients with normal renal and hepatic function.[68] 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.[76]

Clevidipine

Clevidipine is third-generation dihydropyridine calcium-channel blocker that has been developed for use in clinical settings in which tight BP control is crucial.[83] Clevidipine is an ultrashort-acting selective arteriolar vasodilator.[84,85] Clevidipine acts by selectively inhibiting the influx of extracellular calcium through the L-type channel, relaxing smooth muscle of small arteries, and reducing peripheral vascular resistance.[86] Similar to esmolol, it is rapidly metabolized by RBC esterases; thus, its metabolism is not affected by renal or hepatic function. Clevidipine reduces BP by a direct and selective effect on arterioles, thereby reducing afterload without affect-

ing cardiac filling pressures or causing reflex tachycardia.[35] Stroke volume and cardiac output usually increase. Moreover, clevidipine has been shown to protect against ischemia/reperfusion injury in an animal model of myocardial ischemia and to maintain renal function and splanchnic blood flow.[87–89]

Several small trials[90,91] have shown clevidipine to be very effective in the control of postoperative hypertension. Although no studies have investigated the role of this drug in hypertensive emergencies, its profile makes it a potentially ideal drug for this indication. At this time, clevidipine is not available in the United States for use outside of clinical trials.

Nifedipine, nitroglycerin, and hydralazine are not recommended in the management of hypertensive emergencies. The basis of these recommendations are discussed below.

Nifedipine

Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies, severe hypertension associated with chronic renal failure, postoperative hypertension, and pregnancy-induced hypertension. Although nifedipine has been administered via the sublingual route, the drug is poorly soluble and is not absorbed through the buccal mucosa. It is however rapidly absorbed from the GI tract after the capsule is broken/dissolved.[92] This mode of administration has not been approved by the US Food and Drug Administration (FDA). A significant decrease in BP is usually observed 5 to 10 min after nifedipine administration, with a peak effect from 30 to 60 min, and a duration of action of approximately 6 to 8 h.[93]

Sudden uncontrolled and severe reductions in BP accompanying the administration of nifedipine may precipitate cerebral, renal, and myocardial ischemic events that have been associated with fatal outcomes.[94] Elderly hypertensive patients with underlying organ impairment and structural vascular disease are more vulnerable to the rapid and uncontrolled reduction in arterial pressure. 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. The Cardiorenal Advisory Committee of the FDA has concluded that the practice of administering sublingual/oral nifedipine should be abandoned because this agent is not safe nor efficacious.[95]

Nitroglycerin, Hydralazine, and Diuretics

Nitroglycerin is a potent venodilator and only at high doses affects arterial tone.[96] It causes hypotension and reflex tachycardia, which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces BP by reducing preload and cardiac output; undesirable effects in patients with compromised cerebral and renal perfusion. Low-dose administration (approximately 60 mg/min) may, however, be used as an adjunct to IV antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.

Hydralazine is a direct-acting vasodilator. Following IM or IV administration, there is an initial latent period of 5 to 15 min followed by a progressive and often precipitous fall in BP that can last up to 12 h.[97,98] Although the circulating half-life of hydralazine is only approximately 3 h, the half-time of its effect on BP is approximately 10 h.[99,100] Because of the prolonged and unpredictable antihypertensive effects of hydralazine and the inability to effectively titrate its hypotensive effect, it is best avoided in the management of hypertensive crises.

Volume depletion is common in patients with hypertensive emergencies, and the administration of a diuretic together with a hypertensive agent can lead to a precipitous drop in BP. Diuretics should be avoided unless specifically indicated for volume overload, as occurs in renal parenchymal disease or coexisting pulmonary edema.

Special Conditions

Acute Aortic Dissection

Aortic dissection should be considered a likely diagnostic possibility in patients presenting to the emergency department with acute chest pain and elevated BP. Left untreated, approximately three fourths of patients with type A dissection (ascending aorta) die within 2 weeks of an acute episode, but with successful therapy the 5-year survival rate is 75%.[30,101] Hence, timely recognition of this disease entity coupled with urgent and appropriate management is the key to a successful outcome in the majority of these patients. It is important to recognize that the propagation of the dissection is dependent not only on the elevation of the BP itself but also on the velocity of left ventricular ejection.[30,31,101–103]

A vasodilator alone is not ideal in the treatment of acute aortic dissection because this can promote reflex tachycardia, increase aortic ejection velocity, and promote dissection propagation. The combination of a β-adrenergic antagonist and vasodilator is the standard approach to treatment.[30,31] Esmolol is the β-adrenergic antagonist of choice with metoprolol as a suitable alternative.[104,105] Although nitroprus-

side has traditionally been used as the vasodilator of choice, nicardipine or fenoldopam are less toxic, equally effective alternatives.[105,106] All patients with aortic dissection require cardiovascular surgical consultation to determine if surgical management is necessary. Unless significant medical comorbidities are present, surgery is indicated for all patients with type A dissection.[107,108] Patients with type B dissections and distal aortic dissections can be managed with aggressive BP control because outcomes have been shown to be the same with either medical or surgical treatment unless complications such as leak, rupture, or impaired flow to vital organs supervene.[30,31,103]

Cerebrovascular Accidents

The vast majority of patients with cerebral ischemia present with acutely elevated BP regardless of the subtype of infarct or preexisting hypertension.[109,110] The BP elevation decreases spontaneously over time. The elevated BP is not a manifestation of a hypertensive emergency but rather a protective physiologic response to maintain cerebral perfusion pressure to the vascular territory affected by ischemia. Lowering the BP in patients with ischemic strokes may reduce cerebral blood flow, which because of impaired autoregulation, may result in further ischemic injury. The common practice of "normalizing" the BP following a cerebrovascular accident is potentially dangerous. It should be noted that the Intravenous Nimodipine West European Trial for acute stroke was stopped because of increased neurologic deterioration in the treatment group, which the investigators[111,112] attributed to the effects of hypotension.

The American Stroke Association and the European Stroke Initiative guidelines[113,114] recommend withholding antihypertensive therapy for acute ischemic stroke unless there is planned thrombolysis, evidence of concomitant noncerebral acute organ damage, or if the BP is excessively high, arbitrarily chosen as a SBP $>$ 220 mm Hg or a DBP $>$ 120 mm Hg based on the upper limit of normal autoregulation. In these patients, the aim is to reduce the pressure by not more than 10 to 15% in the first 24 h. Semplicini and colleagues[115] demonstrated that a high initial BP was associated with a better neurologic outcome following an acute ischemic stroke. These authors[115] suggests that hypertension may be protective during an acute ischemic stroke and that lowering the BP may be potentially harmful. Indeed, pharmacologic elevation of BP in patients with ischemic stroke is a promising investigational approach. Small studies[116–118] of patients treated with vasopressors and plasma expanders have demonstrated short-term neurologic improvement in 20 to 40% of patients without any adverse effects. These protocols generally call for raising the MAP by 20% or to 130 to 140 mm Hg while keeping the SBP $<$ 200 mm Hg. It is thought that patients with fluctuating deficits, proximal large vessel stenosis or occlusion, or large areas of MRI diffusion-perfusion mismatch are most likely to respond to induced hypertension. In patients receiving thrombolytic therapy, antihypertensive therapy is required for SBP $>$ 185 mm Hg or DBP $>$ 110 mm Hg, with a targeted SBP of 180 mm Hg and a DBP of 105 mm Hg.[113,119,120] The current American Heart Association guidelines[119] recommend the use of labetalol or nicardipine if the SBP is $>$ 220 mm Hg or the DBP is from 121 to 140 mm Hg, and nitroprusside for a DBP $>$ 140 mm Hg. For the reasons outlined above, we believe nitroprusside to be a poor choice in patients with intracranial pathology. The Acute Candesartan Cilexetil Therapy in Stroke Survivors study[121] demonstrated a reduction in 12-month mortality and the number of vascular events in patients with a SBP $>$ 200 mm Hg or a DBP $>$ 110 mm Hg who were treated with an angiotensin type 1 receptor blockade (candesartan cilexetil) immediately after an ischemic stroke. The mechanism(s) by which the angiotensin type 1 receptor blocker exerted its beneficial effects is unclear, as the BP profiles were nearly identical in the treatment and placebo groups. Additional studies are required to confirm the benefit of angiotensin type 1 receptor blockers in patients with ischemic stroke.

In patients with intracerebral hematomas, there is almost always a rise in intracranial pressure with reflex systemic hypertension. There is no evidence that hypertension provokes further bleeding in patients with intracranial hemorrhage. However, a precipitous fall in systemic BP will compromise cerebral perfusion. The controlled lowering of the BP is currently recommended only when the SBP is $>$ 200 mm Hg, the DBP is $>$ 110 mm Hg, or the MAP is $>$ 130 mm Hg.[122–124] A study[125] has demonstrated that the rapid decline of BP within the first 24 h after presentation of an intracranial hemorrhage was associated with increased mortality; the rate of decline in BP was independently associated with increased mortality. Nicardipine has been demonstrated to be an effective agent for the control of BP in patients with intracerebral hemorrhage.[126]

Preeclampsia and Eclampsia

Hypertension is one of the most common medical disorders affecting pregnancy. It complicates 12% of pregnancies and is responsible for 18% of maternal deaths in the United States.[127] The presentation of a patient with pregnancy-induced hypertension may

range from a mild to a life-threatening disease process.[128] Initial therapy of preeclampsia includes volume expansion, magnesium sulfate ($MgSO_4$) for seizure prophylaxis and BP control.[129–131] Delivery is the definitive treatment for preeclampsia and eclampsia.

Magnesium sulfate is usually administered as a loading dose of 4 to 6 g in 100 mL 5% dextrose in 1/4 normal saline solution over 15 to 20 min, followed by a constant infusion of 1 to 2 g/h of $MgSO_4$ depending on urine output and deep tendon reflexes, which are checked on an hourly basis. The next step in the management of preeclampsia is to reduce the BP to a safe range being diligent to avoid significant hypotension. The objective of treating severe hypertension is to prevent intracerebral hemorrhage and cardiac failure without compromising cerebral perfusion or jeopardizing uteroplacental blood flow, which is already reduced in many women with preeclampsia.[128] Studies[132–134] of women with mild preeclampsia have shown no benefit to antihypertensive therapy (labetalol or calcium-channel blockers) and suggested that antihypertensive therapy may increase the risk of intrauterine growth retardation. Antihypertensive therapy is therefore administered primarily to prevent complications in the mother. The Working Group Report on High Blood Pressure in Pregnancy[135] recommends initiation of antihypertensive therapy for a DBP $\geq$ 105 mm Hg. Furthermore, most authorities and the current guidelines from the American College of Obstetricians and Gynecologists[128,135–138] recommend keeping SBP from 140 to 160 mm Hg and DBP from 90 to 105 mm Hg. This recommendation is supported by a study[139] that demonstrated that SBP $>$ 160 mm Hg was the most important factor associated with a cerebrovascular accident in patients with severe preeclampsia and eclampsia. This would suggest that SBP from 155 to 160 mm Hg should be the primary trigger to initiate antihypertensive therapy in a patient with severe preeclampsia or eclampsia.[139,140] It should be noted that patients with preeclampsia/eclampsia may have a very labile BP; this fact together with the narrow target BP range dictate that these patients be closely monitored in an ICU, preferably with an arterial catheter. Intracerebral hemorrhage is a devastating complication in these patients that can be avoided by scrupulous attention to BP control.

No antihypertensive medication is specifically approved by the FDA for use in pregnant women. Hydralazine has been recommended as the drug of choice to treat severe preeclampsia and eclampsia since the early 1970s.[141] However, hydralazine has a number of properties that make it unsuitable for this indication. Its side effects (such as headache, nausea, and vomiting) are common and mimic symptoms of deteriorating preeclampsia. Most importantly, however, it has a delayed onset of action, an unpredictable hypotensive effect, and a prolonged duration of action. These properties may result in a precipitous hypotensive overshoot compromising both maternal cerebral blood flow and uteroplacental blood flow. Indeed, in a metaanalysis published by Magee and colleagues,[142] hydralazine was associated with an increased risk of maternal hypotension that was associated with an excess of cesarean sections, placental abruptions, and low Apgar scores. Based on the available data, we suggest that hydralazine not be used as first-line treatment of severe hypertension in pregnancy. Similarly, sublingual or oral nifedipine should be avoided in this setting. Our preference is IV labetalol or nicardipine, which are easier to titrate and have a more predictable dose response than hydralazine. Both agents appear to be safe and effective in hypertensive pregnant patients.[143–149] Nitroprusside and ACE inhibitors are contraindicated in pregnant patients.

Sympathetic Crises

The most commonly encountered sympathetic crises are related to the recreational use of sympathomimetic drugs such as cocaine, amphetamine, or phencyclidine. Rarely, these crises may be seen with pheochromocytoma, patients receiving a monoamine oxidase inhibitor who ingest a tyramine-containing food, or patients who abruptly stop antihypertensive medications such as clonidine or β-adrenergic antagonists.

In the clinical situations characterized by sympathetic overstimulation, β-adrenergic antagonists should be avoided to prevent vascular β-receptor antagonism resulting in unopposed α-adrenergic activity and potential increase in BP. In fact, in cocaine-induced hypertensive emergency, the use of β-adrenergic blockade can increase coronary vasoconstriction, fail to control heart rate, increase BP, and decrease survival.[150–152] Interestingly, although labetalol is traditionally considered the ideal agent due to its α- and β-adrenergic antagonism, experimental studies[153–157] do not support its use in this clinical setting. BP control is best achieved with nicardipine, fenoldopam, or verapamil in combination with a benzodiazepine.[152,158,159] Phentolamine is an alternative agent.[160]

Acute Postoperative Hypertension

Acute postoperative hypertension (APH) has been defined as a significant elevation in BP during the immediate postoperative period that may lead to serious neurologic, cardiovascular, or surgical-site

complications and that requires urgent management.[161] Despite the widespread and long-standing recognition of APH, there is no agreement in the literature on a more precise quantitative definition.[161–163] APH has an early onset, being observed within 2 h after surgery in most cases and is typically of short duration, with most patients requiring treatment for ≤ 6 h. Postoperative complications of APH may include hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmia, congestive cardiac failure with pulmonary edema, failure of vascular anastomoses, and bleeding at the surgical site. Although APH may occur following any major surgery, it is most commonly associated with cardiothoracic, vascular, head and neck, and neurosurgical procedures. The pathophysiologic mechanism underlying APH is uncertain and may vary with the surgical procedure and other factors. However, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with APH.[17] The primary hemodynamic alteration observed in APH is an increase in afterload with an increase in SBP and DBP with or without tachycardia.

There is no consensus concerning the treatment threshold for the management of noncardiac surgery patients with APH. Treatment is frequently a bedside decision by the anesthesiologist or surgeon that takes into consideration the baseline BP, concomitant disease, and the perceived risk of complications. In contrast, in cardiac surgery patients, treatment is recommended for a BP > 140/90 or a MAP of at least 105 mm Hg.[161–163] Pain and anxiety are common contributors to BP elevations and should be treated before administration of antihypertensive therapy. Other potentially reversible causes of APH include hypothermia with shivering, hypoxemia, hypercarbia, and bladder distension. Short-term administration of a short-acting IV agent is recommended when there is no identifiable treatable cause of hypertension. Labetalol, esmolol, nicardipine, and clevidipine have proven effective in the management of APH.[90,91,161,164–168]

Conclusions

Patients with hypertensive emergencies require the immediate reduction of the elevated BP to prevent and arrest progressive end-organ damage. The best clinical setting to achieve this BP control is in the ICU, with the use of titratable IV hypotensive agents. There are several antihypertensive agents available including esmolol, nicardipine, labetalol, and fenoldopam. While sodium nitroprusside is a rapid-acting and potent antihypertensive agent, it may be associated with significant toxicity and should therefore be used in select circumstances at a dose not to exceed 2 μg/kg/min. The appropriate therapeutic approach of each patient will depend on the clinical presentation of the patient. Agents such as nifedipine and hydralazine should be abandoned because these agents are associated with significant toxicities and/or side effect profile.

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References

1 Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA 2003; 290:199–206
2 Chobanian AV, Bakris GL, Black HR, et al. The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289:2560–2572
3 The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1993; 153:154–183
4 Joint National Committee for the Detection, Evaluation and Treatment of High Blood Pressure: the 1984 report. Arch Intern Med 1984; 114:1045–1057
5 Volhard F, Fahr T. Die brightsche Nierenkranbeit: Klinik, Pathologie und Atlas. Berlin, Germany: Springer, 1914
6 Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1939; 197:332–343
7 Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Am J Hypertens 2001; 14:837–854
8 McRae RPJ, Liebson PR. Hypertensive crisis. Med Clin North Am 1986; 70:749–767
9 Vidt DG. Current concepts in treatment of hypertensive emergencies. Am Heart J 1986; 111:220–225
10 Bennett NM, Shea S. Hypertensive emergency: case criteria, sociodemographic profile, and previous care of 100 cases. Am J Public Health 1988; 78:636–640
11 Potter JF. Malignant hypertension in the elderly. Q J Med 1995; 88:641–647
12 Vital and health statistics: detailed diagnoses and procedures for patients discharged from short-stay hospitals: United States, 1983–1990. Hyattsville, MD: National Center for Health Statistics, 1997
13 Tisdale JE, Huang MB, Borzak S, et al. Risk factors for hypertensive crisis: importance of out-patient blood pressure control. Fam Pract 2004; 21:420–424
14 Shea S, Misra D, Ehrlich MH, et al. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. N Engl J Med 1992; 327:776–781
15 Tumlin JA, Dunbar LM, Oparil S, et al. Fenoldopam, a dopamine agonist, for hypertensive emergency: a multicenter randomized trial: fenoldopam Study Group. Acad Emerg Med 2000; 7:653–662
16 Ault MJ, Ellrodt AG. Pathophysiological events leading to the end-organ effects of acute hypertension. Am J Emerg Med 1985; 3:10–15
17 Wallach R, Karp RB, Reves JG, et al. Pathogenesis of

paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol 1980; 46:559–565
18 Funakoshi Y, Ichiki T, Ito K, et al. Induction of interleukin-6 expression by angiotensin II in rat vascular smooth muscle cells. Hypertension 1999; 34:118–125
19 Han Y, Runge MS, Brasier AR. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-κ B transcription factors. Circ Res 1999; 84:695–703
20 Zampaglione B, Pascale C, Marchisio M, et al. Hypertensive urgencies and emergencies: prevalence and clinical presentation. Hypertension 1996; 27:144–147
21 Varon J, Marik PE. The diagnosis and management of hypertensive crises. Chest 2000; 118:214–227
22 Rey E, LeLorier J, Burgess E, et al. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. Can Med Assoc J 1997; 157:1245–1254
23 Graves JW. Prevalence of blood pressure cuff sizes in a referral practice of 430 consecutive adult hypertensives. Blood Press Monit 2001; 6:17–20
24 Linfors EW, Feussner JR, Blessing CL, et al. Spurious hypertension in the obese patient: effect of sphygmomanometer cuff size on prevalence of hypertension. Arch Intern Med 1984; 144:1482–1485
25 Hickler RB. "Hypertensive emergency": a useful diagnostic category. Am J Public Health 1988; 78:623–624
26 Garcia JYJ, Vidt DG. Current management of hypertensive emergencies. Drugs 1987; 34:263–278
27 Fromm RE, Varon J, Gibbs L. Congestive heart failure and pulmonary edema for the emergency physician. J Emerg Med 1995; 13:71–87
28 Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001; 344:17–22
29 Strandgaard S, Olesen J, Skinhoj E, et al. Autoregulation of brain circulation in severe arterial hypertension. BMJ 1973; 1:507–510
30 Khan IA, Nair CK. Clinical, diagnostic, and management perspectives of aortic dissection. Chest 2002; 122:311–328
31 Estrera AL, Miller CC III, Safi HJ, et al. Outcomes of medical management of acute type B aortic dissection. Circulation 2006; 114:I384–I389
32 Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med 2003; 348:1756–1763
33 DiPette DJ, Ferraro JC, Evans RR, et al. Enalaprilat, an intravenous angiotensin-converting enzyme inhibitor, in hypertensive crises. Clin Pharmacol Ther 1985; 38:199–204
34 Hirschl MM, Binder M, Bur A, et al. Impact of the renin-angiotensin-aldosterone system on blood pressure response to intravenous enalaprilat in patients with hypertensive crises. J Hum Hypertens 1997; 11:177–183
35 Nordlander M, Bjorkman JA, Regard HCG, et al. Pharmacokinetics and hemodynamic effects of an ultrashort-acting calcium antagonist [abstract]. Br J Anaesth 1996; 76 (suppl): A24
36 Lund-Johansen P. Pharmacology of combined α-β-blockade: II. Haemodynamic effects of labetalol. Drugs 1984; 28(suppl 2):35–50
37 Kanot J, Allonen H, Kleimola T, et al. Pharmacokinetics of labetalol in healthy volunteers. Int J Clin Pharmacol Ther Toxicol 1981; 19:41–44
38 Goldberg ME, Clark S, Joseph J, et al. Nicardipine versus placebo for the treatment of postoperative hypertension. Am Heart J 1990; 119:446–450
39 Pearce CJ, Wallin JD. Labetalol and other agents that block both α- and β-adrenergic receptors. Cleve Clin J Med 1994; 61:59–69
40 Wallin JD. Adrenoreceptors and renal function. J Clin Hyperten 1985; 1:171–178
41 Marx PG, Reid DS. Labetalol infusion in acute myocardial infarction with systemic hypertension. Br J Clin Pharmacol 1979; 8:233S–238S
42 Olsen KS, Svendsen LB, Larsen FS, et al. Effect of labetalol on cerebral blood flow, oxygen metabolism and autoregulation in healthy humans. Br J Anaesth 1995; 75:51–54
43 Rosei EA, Trust PM, Brown JJ. Intravenous labetalol in severe hypertension. Lancet 1975; 2:1093–1094
44 Schillinger D. Nifedipine in hypertensive emergencies: a prospective study. J Emerg Med 1987; 5:463–473
45 Lambert CR, Hill JA, Feldman RL, et al. Effects of nicardipine on exercise- and pacing-induced myocardial ischemia in angina pectoris. Am J Cardiol 1987; 60:471–476
46 Lambert CR, Hill JA, Nichols WW, et al. Coronary and systemic hemodynamic effects of nicardipine. Am J Cardiol 1985; 55:652–656
47 Vincent JL, Berlot G, Preiser JC, et al. Intravenous nicardipine in the treatment of postoperative arterial hypertension. J Cardiothorac Vasc Anesth 1997; 11:160–164
48 Lambert CR, Hill JA, Feldman RL, et al. Effects of nicardipine on left ventricular function and energetics in man. Int J Cardiol 1986; 10:237–250
49 Gray RJ. Managing critically ill patients with esmolol: an ultra short-acting β-adrenergic blocker. Chest 1988; 93: 398–403
50 Lowenthal DT, Porter RS, Saris SD, et al. Clinical pharmacology, pharmacodynamics and interactions with esmolol. Am J Cardiol 1985; 56:14F–18F
51 Reynolds RD, Gorczynski RJ, Quon CY. Pharmacology and pharmacokinetics of esmolol. J Clin Pharmacol 1986; 26(suppl):A3–A14
52 Balser JR, Martinez EA, Winters BD. et al. β-Adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. Anesthesiol 1998; 89:1052–1059
53 Platia EV, Michelson EL, Porterfield JK, et al. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. Am J Cardiol 1989; 63:925–929
54 Stumpf JL. Drug therapy of hypertensive crises. Clin Pharm 1988; 7:582–591
55 Smerling A, Gersony WM. Esmolol for severe hypertension following repair of aortic coarctation. Crit Care Med 1990; 18:1288–1290
56 Gray RJ, Bateman TM, Czer LS, et al. Use of esmolol in hypertension after cardiac surgery. Am J Cardiol 1985; 56:49F–56F
57 Gray RJ, Bateman TM, Czer LS, et al. Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. Am J Cardiol 1987; 59:887–891
58 Muzzi DA, Black S, Losasso TJ, et al. Labetalol and esmolol in the control of hypertension after intracranial surgery. Anesth Analg 1990; 70:68–71
59 Bodmann KF, Troster S, Clemens R, et al. Hemodynamic profile of intravenous fenoldopam in patients with hypertensive crisis. Clin Investig 1993; 72:60–64
60 Munger MA, Rutherford WF, Anderson L, et al. Assessment of intravenous fenoldopam mesylate in the management of severe systemic hypertension. Crit Care Med 1990; 18:502–504
61 White WB, Radford MJ, Gonzalez FM, et al. Selective dopamine-1 agonist therapy in severe hypertension: effects of intravenous fenoldopam. J Am Coll Cardiol 1988; 11: 1118–1123

62 Shusterman NH, Elliott WJ, White WB. Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. Am J Med 1993; 95:161–168
63 Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. Circulation 1990; 81:970–977
64 White WB, Halley SE. Comparative renal effects of intravenous administration of fenoldopam mesylate and sodium nitroprusside in patients with severe hypertension. Arch Intern Med 1989; 149:870–874
65 Ng TM, Shurmur SW, Silver M, et al. Comparison of N-acetylcysteine and fenoldopam for preventing contrast-induced nephropathy (CAFCIN). Int J Cardiol 2006; 109: 322–328
66 Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA 2006; 295:2765–2779
67 Friederich JA, Butterworth JF. Sodium nitroprusside: twenty years and counting. Anesth Analg 1995; 81:152–162
68 Robin ED, McCauley R. Nitroprusside-related cyanide poisoning: time (long past due. for urgent, effective interventions: chest 1992; 102:1842–1845
69 Hartmann A, Buttinger C, Rommel T, et al. Alteration of intracranial pressure, cerebral blood flow, autoregulation and carbon dioxide-reactivity by hypotensive agents in baboons with intracranial hypertension. Neurochirurgia 1989; 32:37–43
70 Kondo T, Brock M, Bach H. Effect of intra-arterial sodium nitroprusside on intracranial pressure and cerebral autoregulation. Jpn Heart J 1984; 25:231–237
71 Griswold WR, Reznik V, Mendoza SA. Nitroprusside-induced intracranial hypertension [letter]. JAMA 1981; 246: 2679–2680
72 Anile C, Zanghi F, Bracali A, et al. Sodium nitroprusside and intracranial pressure. Acta Neurochir 1981; 58:203–211
73 Mann T, Cohn PF, Holman LB, et al. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease: results in 25 patients and comparison with nitroglycerin. Circulation 1978; 57:732–738
74 Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. N Engl J Med 1982; 306:1129–1135
75 Pasch T, Schulz V, Hoppenshauser G. Nitroprusside-induced formation of cyanide and its detoxication with thiosulphate during deliberate hypotension. J Cardiovasc Pharmacol 1983; 5:77–85
76 Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulphate prophylaxis. Am J Crit Care 1992; 2:19–27
77 Niknahad H, O'Brien PJ. Involvement of nitric oxide in nitroprusside-induced hepatocyte cytotoxicity. Biochem Pharmacol 1996; 51:1031–1039
78 Izumi Y, Benz AM, Clifford DB, et al. Neurotoxic effects of sodium nitroprusside in rat hippocampal slices. Exp Neurol 1993; 121:14–23
79 Vesey CJ, Cole PV, Simpson PJ. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. Br J Anaesth 1976; 48:651–659
80 Nakamura Y, Yasuda M, Fujimori H, et al. Cytotoxic effect of sodium nitroprusside on PC12 cells. Chemosphere 1997; 34:317–324
81 Gobbel GT, Chan TY, Chan PH. Nitric oxide- and superoxide-mediated toxicity in cerebral endothelial cells. J Pharmacol Exp Ther 1997; 282:1600–1607
82 Rauhala P, Khaldi A, Mohanakumar KP, et al. Apparent role of hydroxyl radicals in oxidative brain injury induced by sodium nitroprusside. Free Radic Biol Med 1998; 24:1065–1073
83 Rodriguez G, Varon J. Clevidipine: a unique agent for the critical care practitioner. Crit Care Shock 2006; 9:9–15
84 Bailey JM, Lu W, Levy JH, et al. Clevidipine in adult cardiac surgical patients: a dose-finding study. Anesthesiol 2002; 96:1086–1094
85 Ericsson H, Fakt C, Jolin-Mellgard A, et al. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol 1999; 47:531–538
86 Ericsson H, Tholander B, RegardH CG. *In vitro* hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting calcium antagonist metabolised by esterases, in different animal species and man. Eur J Pharmaceut Sci 1999; 8:29–37
87 Segawa D, Sjoquist PO, Wang QD, et al. Time-dependent cardioprotection with calcium antagonism and experimental studies with clevidipine in ischemic-reperfused pig hearts: part II. J Cardiovasc Pharmacol 2002; 40:339–345
88 Segawa D, Sjoquist PO, Wang QD, et al. Calcium antagonist protects the myocardium from reperfusion injury by interfering with mechanisms directly related to reperfusion: an experimental study with the ultrashort-acting calcium antagonist clevidipine. J Cardiovasc Pharmacol 2000; 36:338–343
89 Stephens CT, Jandhyala BS. Effects of fenoldopam, a dopamine D-1 agonist, and clevidipine, a calcium channel antagonist, in acute renal failure in anesthetized rats. Clin Exp Hypertension 2002; 24:301–313
90 Powroznyk AV, Vuylsteke A, Naughton C, et al. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesthesiol 2003; 20:697–703
91 Kieler-Jensen N, Jolin-Mellgard A, Nordlander M, et al. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand 2000; 44:186–193
92 van Harten J, Burggraaf K, Danhof M, et al. Negligible sublingual absorption of nifedipine. Lancet 1987; 2:1363–1365
93 Huysmans FT, Sluiter HE, Thien TA, et al. Acute treatment of hypertensive crisis with nifedipine. Br J Clin Pharmacol 1983; 16:725–727
94 Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA 1996; 276:1328–1331
95 Levy JH. Treatment of perioperative hypertension. Anesthesiol Clin North Am 1999; 17:569–570
96 Bussmann WD, Kenedi P, von Mengden HJ, et al. Comparison of nitroglycerin with nifedipine in patients with hypertensive crisis or severe hypertension. Clin Investig 1992; 70:1085–1088
97 Schroeder HA. Effects on hypertension of sulfhydryl and hydrazine compounds. J Clin Invest 1951; 30:672–673
98 Shepherd AM, Ludden TM, McNay JL, et al. Hydralazine kinetics after single and repeated oral doses. Clin Pharmacol Ther 1980; 28:804–811
99 O'Malley K, Segal JL, Israili ZH, et al. Duration of hydralazine action in hypertension. Clin Pharmacol Ther 1975; 18:581–586
100 Ludden TM, Shepherd AM, McNay JL, et al. Hydralazine kinetics in hypertensive patients after intravenous administration. Clin Pharmacol Ther 1980; 28:736–742

101 Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. N Engl J Med 1997; 336:1876–1888
102 Cohn LH. Aortic dissection: new aspects of diagnosis and treatment. Hosp Pract 1994; 29:47–56
103 Chen K, Varon J, Wenker OC, et al. Acute thoracic aortic dissection: the basics. J Emerg Med 1997; 15:859–867
104 O'Connor B, Luntley JB. Acute dissection of the thoracic aorta: esmolol is safer than and as effective as labetalol [letter]. BMJ 1995; 310:875
105 Hoshino T, Ohmae M, Sakai A. Spontaneous resolution of a dissection of the descending aorta after medical treatment with a β blocker and a calcium antagonist. Br Heart J 1987; 58:82–84
106 Iguchi A, Tabayashi K. Outcome of medically treated Stanford type B aortic dissection. Jpn Circ J 1998; 62:102–105
107 Pitt MP, Bonser RS. The natural history of thoracic aortic aneurysm disease: an overview. J Card Surg 1997; 12:270–278
108 Borst HG, Laas J. Surgical treatment of thoracic aortic aneurysms. Adv Card Surg 1993; 4:47–87
109 Wallace JD, Levy LL. Blood pressure after stroke. JAMA 1981; 246:2177–2180
110 Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986; 17:861–864
111 Wahlgren NG, MacMohon DG, De Keyser J, et al. The Intravenous Nimodipine West Europen Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. Cerebrovasc Dis 1994; 4:204–210
112 Ahmed N, Nasman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke 2000; 31:1250–1255
113 Adams HP Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003; 34:1056–1083
114 The European Stroke Initiative Executive Committee and the EUSI Writing Committee. European Stroke Initiative recommendations for stroke management: update 2003. Cerebrovasc Dis 2003; 16:311–337
115 Semplicini A, Maresca A, Boscolo G, et al. Hypertension in acute ischemic stroke: a compensatory mechanism or an additional damaging factor? Arch Intern Med 2003; 163: 211–216
116 Rordorf G, Koroshetz WJ, Ezzeddine MA, et al. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology 2001; 56:1210–1213
117 Rordorf G, Cramer SC, Efird JT, et al. Pharmacological elevation of blood pressure in acute stroke: clinical effects and safety. Stroke 1997; 28:2133–2138
118 Hillis AE, Ulatowski JA, Barker PB, et al. A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. Cerebrovasc Dis 2003; 16:236–246
119 Adams H, Adams R, Del ZG, et al. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update; a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke 2005; 36:916–923
120 NINDS rtPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581–1587
121 Schrader J, Luders S, Kulschewski A, et al. The ACCESS study: evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke 2003; 34:1699–1703
122 Lavin P. Management of hypertension in patients with acute stroke. Arch Intern Med 1986; 146:66–68
123 Hirschl MM. Guidelines for the drug treatment of hypertensive crises. Drugs 1995; 50:991–1000
124 O'Connell J, Gray C. Treating hypertension after stroke. BMJ 1994; 308:1523–1524
125 Qureshi AI, Bliwise DL, Bliwise NG, et al. Rate of 24-hour blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. Crit Care Med 1999; 27:480–485
126 Qureshi AI, Harris-Lane P, Kirmani JF, et al. Treatment of acute hypertension in patients with intracerebral hemorrhage using American Heart Association guidelines. Crit Care Med 2006; 34:1975–1980
127 Koonin LM, MacKay AP, Berg CJ, et al. Pregnancy-related mortality surveillance–United States, 1987–1990. Morb Mortal Wkly Rep 1997; CDC Surveillance Summaries 46: 17–36
128 Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol 2005; 105:402–410
129 Belfort MA, Anthony J, Saade GR, et al. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003; 348:304–311
130 Coetzee EJ, Dommisse J, Anthony J. A randomised controlled trial of intravenous magnesium sulphate versus placebo in the management of women with severe pre-eclampsia. Br J Obstet Gynaecol 1998; 105:300–303
131 Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995; 333:201–205
132 Sibai BM, Gonzalez AR, Mabie WC, et al. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol 1987; 70:323–327
133 Sibai BM, Barton JR, Akl S, et al. A randomized prospective comparison of nifedipine and bed rest versus bed rest alone in the management of preeclampsia remote from term. Am J Obstet Gynecol 1992; 167:879–884
134 von DP, Ornstein MP, Bull SB, et al. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 2000; 355:87–92
135 Gifford RW, August PA, Cunningham G. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000; 183:S1–22
136 National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000; 183:S1–S22
137 Diagnosis and management of preeclampsia and eclampsia: ACOG Practice Bulletin No. 33. American College of Obstetricians and Gynecologists. Obstet Gynecol 2002; 99: 159–167
138 Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004; 103:981–991
139 Martin JN Jr, Thigpen BD, Moore RC, et al. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol 2005; 105: 246–254
140 Cunningham FG. Severe preeclampsia and eclampsia: systolic hypertension is also important. Obstet Gynecol 2005; 105:237–238
141 Hellman LM, Pritchard JA. Williams obstetrics, 14th ed. New York, NY: Appleton-Century-Crofts, 1971
142 Magee LA, Cham C, Waterman EJ, et al. Hydralazine for

treatment of severe hypertension in pregnancy: meta-analysis. BMJ 2003; 327:955–960
143 Pickles CJ, Broughton PF, Symonds EM. A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension. Br J Obstet Gynaecol 1992; 99:964–968
144 Pickles CJ, Symonds EM, Pipkin FB. The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension. Br J Obstet Gynaecol 1989; 96:38–43
145 Mabie WC, Gonzalez AR, Sibai BM, et al. A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. Obstet Gynecol 1987; 70:328–333
146 Jannet D, Carbonne B, Sebban E, et al. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol 1994; 84:354–359
147 Carbonne B, Jannet D, Touboul C, et al. Nicardipine treatment of hypertension during pregnancy. Obstet Gynecol 1993; 81:908–914
148 Hanff LM, Vulto AG, Bartels PA, et al. Intravenous use of the calcium-channel blocker nicardipine as second-line treatment in severe, early-onset pre-eclamptic patients. J Hypertension 2005; 23:2319–2326
149 Elatrous S, Nouira S, Ouanes BL, et al. Short-term treatment of severe hypertension of pregnancy: prospective comparison of nicardipine and labetalol. Intensive Care Med 2002; 28:1281–1286
150 Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by β-adrenergic blockade. Ann Intern Med 1990; 112:897–903
151 Pitts WR, Lange RA, Cigarroa JE, et al. Cocaine-induced myocardial ischemia and infarction: pathophysiology, recognition, and management. Prog Cardiovasc Dis 1997; 40: 65–76
152 Hollander JE. The management of cocaine-associated myocardial ischemia. N Engl J Med 1995; 333:1267–1272
153 Gay GR, Loper KA. The use of labetalol in the management of cocaine crisis. Ann Emerg Med 1988; 17:282–283
154 Dusenberry SJ, Hicks MJ, Mariani PJ. Labetalol treatment of cocaine toxicity [letter]. Ann Emerg Med 1987; 16:235
155 Spivey WH, Schoffstall JM, Kirkpatrick R, et al. Comparison of labetalol, diazepam, and haloperidol for the treatment of cocaine toxicity in a swine mode [abstract]. Ann Emerg Med 1990; 19:467–468
156 Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. J Pharmacol Exp Ther 1981; 217:350–356
157 Boehrer JD, Moliterno DJ, Willard JE, et al. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. Am J Med 1993; 94:608–610
158 Negus BH, Willard JE, Hillis LD, et al. Alleviation of cocaine-induced coronary vasoconstriction with intravenous verapamil. Am J Cardiol 1994; 73:510–513
159 Moore NA, Rees G, Sanger G, et al. Effect of L-type calcium channel modulators on stimulant-induced hyperactivity. Neuropharmacology 1993; 32:719–720
160 Hollander JE, Carter WA, Hoffman RS. Use of phentolamine for cocaine-induced myocardial ischemia [letter]. N Engl J Med 1992; 327:361
161 Haas CE, LeBlanc JM, Haas CE, et al. Acute postoperative hypertension: a review of therapeutic options. Am J Health System Pharm 2004; 61:1661–1673
162 Cheung AT. Exploring an optimum intra/postoperative management strategy for acute hypertension in the cardiac surgery patient. J Card Surg 2006; 21(suppl 1):S8–S14
163 Weant KA, Flynn JD, Smith KM. Postoperative hypertension. Orthopedics 2004; 27:1159–1161
164 Kwak YL, Oh YJ, Bang SO, et al. Comparison of the effects of nicardipine and sodium nitroprusside for control of increased blood pressure after coronary artery bypass graft surgery. J Int Med Res 2004; 32:342–350
165 Halpern NA, Sladen RN, Goldberg JS, et al. Nicardipine infusion for postoperative hypertension after surgery of the head and neck. Crit Care Med 1990; 18:950–955
166 Halpern NA, Alicea M, Krakoff LR, et al. Postoperative hypertension: a prospective, placebo-controlled, randomized, double-blind trial, with intravenous nicardipine hydrochloride. Angiology 1990; 41:992–1004
167 Halpern NA, Goldberg M, Neely C, et al. Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. Crit Care Med 1992; 20:1637–1643
168 Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharmacokinet 1995; 28:190–202

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