Curr Hypertens Rep (2014) 16:450
DOI 10.1007/s11906-014-0450-z

HYPERTENSIVE EMERGENCIES (BM BAUMANN, SECTION EDITOR)

Current and Newer Agents for Hypertensive Emergencies

Alan Padilla Ramos · Joseph Varon

Published online: 27 May 2014

Abstract Hypertension is an increasingly prevalent chronic illness. The condition may present as a hypertensive crisis, and this entity may be further categorized as either hypertensive emergency or urgency. As the presentation is quite variable and is dependent upon the specific end-organ injury, a thorough history and examination are necessary. Once the underlying pathology is known, a target blood pressure can be determined and a specific therapeutic agent selected. The choice of most appropriate agent must take into consideration coexisting morbidities, desired rate of blood pressure decline, monitoring capabilities of the environment, and experience of the clinician. In hypertensive emergencies, the therapeutic goal is to protect remaining end-organ function, reduce the risk of complications, and thereby improve patient outcomes. This article reviews commonly used antihypertensive medications as well as evidence-based recommendations for state-of-the-art treatment for hypertensive emergencies.

Keywords Hypertension · Hypertensive crisis · Hypertensive emergency · Hypertensive urgency · Blood pressure control · Nicardipine · Clevidipine · Labetalol · Clinical trials

This article is part of the Topical Collection on *Hypertensive Emergencies*

A. Padilla Ramos
Universidad Autonoma de Baja California, Mexicali Campus, Mexicali, Mexico

J. Varon
University General Hospital, Houston, TX, USA

J. Varon
The University of Texas Health Science Center at Houston, Houston, TX, USA

J. Varon
The University of Texas Medical Branch at Galveston, Galveston, TX, USA

A. Padilla Ramos · J. Varon
Dorrington Medical Associates, PA, Houston, TX, USA

J. Varon (✉)
2219 Dorrington Street, Houston, TX 77030, USA
e-mail: joseph.varon@uth.tmc.edu

Introduction

Hypertension remains a major health problem in the United States, affecting nearly 30 % of the population over 20 years of age [1]. Between 2005 and 2008, 68 million Americans met the criteria for diagnosis of hypertension [2]. The clinical entity is not uniformly distributed among the population, occurring twice as often in black compared to white Americans, and more commonly in men than women [3, 4]. The World Health Organization has estimated that by the year 2025, the number of individuals with hypertension will have risen to 1 billion or greater, and that at least 1 % of these patients will experience an acute hypertensive episode requiring hospitalization [5].

Hypertensive emergencies were first described in 1914 in patients with severe hypertension and signs of vascular damage to the heart, brain, kidney, and retina [6]. These individuals usually had a fatal course ending in myocardial infarction, stroke, or renal failure. Keith and colleagues published the first description of the natural history of hypertensive emergencies, reporting a one-year mortality rate in excess of 79 % and median survival of 10.5 months if untreated [7].

Before the development of effective antihypertensive therapy, up to 7 % of hypertensive patients had at least one episode of hypertensive emergency, and today, despite advances in treatment, 1–2 % of patients will have an episode in their

lifetime. In 2025, assuming that estimates for world population and hypertension prevalence remain stable, more than 47 million patients will develop a hypertensive emergency.

Definition of Hypertensive Crisis

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined hypertensive crisis as a systolic blood pressure (SBP) level≥180 mmHg and/or a diastolic blood pressure (DBP) level ≥120 mmHg [8]. Hypertensive crisis is further divided into two categories based upon evidence of target-organ damage. If end-organ damage is present, the condition is classified as hypertensive emergency. Hypertensive crisis without evidence of organ damage is classified as hypertensive urgency. This differentiation has a profound impact on implications for treatment and prognosis. As these entities were not addressed in the more recent JNC-8, current recommendations are based on JNC-7 guidelines, subspecialty consensus statements, and recent clinical trial data [9•].

Hypertensive Emergencies

As noted above, hypertensive emergencies are characterized by elevation of BP accompanied by target-organ dysfunction. Evidence of organ dysfunction is not common in patients with a DBP <130 mmHg (excluding pregnant patients and children). Upon diagnosis, immediate action must ensue to reduce BP as soon as possible. However, BP reduction should be made in a controlled fashion, and not aimed at normalizing the BP, as this can exacerbate target-organ damage [10–12]. Parenteral drug therapy and intensive-care monitoring are critical for the patient who presents with complications such as hypertensive encephalopathy, aortic dissection, acute myocardial infarction, and acute kidney injury (Table 1). While patients who develop hypertensive emergencies typically have chronically elevated BP, this can be a de novo presentation if the patient suffers conditions such as preeclampsia or acute glomerulonephritis [10–13]. The BP level itself may not be as important as the rate of elevation, [14] and a patient with a chronic history of hypertension can tolerate higher levels than a previously normotensive patient [10, 15].

Hypertensive Urgencies

Hypertensive urgencies are severe elevations of BP with no target-organ dysfunction. A majority of these patients present as a result of noncompliance or inadequate treatment [16]. In these individuals, BP control can be achieved over several hours. It is suggested to reduce BP over a period of 24–48 hours with oral medications, usually a short-acting agent (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker), followed by several hours of observation [9•].

Table 1 Examples of Hypertensive Crises

Eclampsia	Severe pre-eclampsia
HELLP Syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets)	Acute coronary syndrome
Acute renal failure	Dissecting aortic aneurysm
Acute postoperative hypertension	Acute left ventricle failure with pulmonary edema
Hypertensive encephalopathy	Acute myocardial infarction/ unstable angina pectoris
Intracerebral hemorrhage	Pulmonary edema with respiratory failure
Microangiopathic hemolytic anemia	

Pathophysiology and Choice of Antihypertensive Agent

Determining the appropriate antihypertensive agent requires an understanding of the pathophysiology of hypertension. Regardless of etiology, the common mediator in all of these crises is humorally mediated peripheral vasoconstriction, and while the most common cause is medication non-compliance, other factors can trigger this response. This vasoconstriction leads to endothelial injury, and activation of platelet and coagulation cascade [17]. The latter deposit of fibrin may explain why, with marked elevations of the BP, fibrinoid necrosis may follow. This chain of events can lead to ischemia, and consequently further release of vasoactive mediators [18]. Excessive renin production by the kidneys stimulates production of angiotensin II, which further increases vascular resistance and the production of proinflammatory cytokines, raising systemic BP [19]. Other factors such as endothelial dysfunction, platelet aggregation, and reactive oxygen species lead to vasoconstriction by decreasing the production of nitric oxide, and in doing so, inhibiting small-vessel dilation [18].

Clinical Presentation and Initial Evaluation

Chronic hypertension is the most common precipitating factor in hypertensive emergency [13], and the presentation is directly related to the particular end-organ that is being affected [12]. Some authors have reported common presenting symptoms of chest pain, followed by dyspnea and neurologic deficits [20]. When a patient presents with a hypertensive crisis, particular consideration should be given to prior BP

control, anti-hypertensive medications (including last dose), and use of recreational drugs in the history of the present illness [12]. The physical examination must include serial BP measurements in both arms, lung and heart auscultation, renal artery auscultation, neurologic evaluation, and fundoscopic evaluation [20, 21]. Symptoms that are as vague as headache or altered mental status can indicate hypertensive encephalopathy [22]. If the patient presents with severe chest or back pain and unequal pulses in the upper extremities, aortic dissection is a major concern, and imaging studies should be obtained as soon as possible to rule out this pathology [23–25]. Electrocardiogram and cardiac enzymes are a part of the initial workup in patients that have shortness of breath or chest pain [26]. A 2D echocardiogram is useful if acute cardiac failure (or exacerbation of chronic cardiac failure) is suspected [27].

Initial Management

As altered auto-regulation is present in hypertensive emergencies, a continuous infusion of a short-acting titratable antihypertensive agent is the preferred method of treatment to prevent further damage [10–12, 28, 29••]. Intensive care unit (ICU) monitoring and, in some patients, intra-arterial BP monitoring is prudent [30]. There is no consensus with regard to first-line agent, and the choice is dictated by the affected target-organ. The goal is to reduce BP by 10–15 % over a period of 30–60 minutes, with the exception of the patient that presents with aortic dissection or acute intracranial bleed, in whom BP must be reduced within 5–10 minutes or to a target SBP <140 mmHg and mean arterial pressure <80 mmHg [31•, 32•].

Pharmacologic Agents

There are a variety of agents that are recommended for patients presenting with a hypertensive emergency [30]. The following drugs are presented with a focus on mechanism of action and trials that led to the proposed use, in no specific order [33•].

Direct Vasodilators

Hydralazine An older antihypertensive agent, hydralazine has a greater effect on the diastolic than the systolic BP [34]. It is short-acting and increases renal blood flow [35]. The onset of action is 5–25 minutes, with a half-life of three hours, but its effect on BP is much longer (up to 12 hours). While it is a good option for patients with impaired renal function, it should not be used in patients with aortic aneurysm or with potential ischemic heart disease, as it increases myocardial contractility. Although commonly used in the past and still recommended in texts, hydralazine is an agent that some suggest should be avoided in pregnancy due to potential maternal-fetal complications, including decreased uteroplacental blood flow [36].

Fenoldopam This drug acts on the peripheral dopamine-1 receptors, causing renal artery vasodilation by activating this receptor on the proximal and distal tubes [35]. It is metabolized in the liver without cytochrome P450 enzyme involvement. The renal effects promote natriuresis (inhibiting sodium reabsorption) and therefore diuresis [37]. Fenoldopam has an onset of action of five minutes and peak action at 15 minutes. The effect lasts from 30–60 minutes, and the half-life is five minutes [38, 39]. The initial dose is 0.1 μg/kg/min, and this can be increased by 0.05–0.1 μg/kg/min to a maximum dose of 1.6 μg/kg/min. Side effects included tachycardia and increased intraocular pressure. As such, it is not the agent of choice in patients with myocardial ischemia, glaucoma, or intracranial hypertension. Another caveat is that this agent is mixed in a solution that contains sodium met bisulfate, and allergic reactions have been reported [10–12, 29••].

Nitrates

Sodium nitroprusside This agent was considered the gold-standard in the past [40]. It is an arterial and venous vasodilator that decreases both afterload and preload. The IV infusion is initiated at 0.25–0.3 mcg/kg/min and may be increased by 0.5 mcg/kg/min until reaching goal BP. It has a rapid onset of action (seconds), duration of 1–2 minutes, and a similar half-life [41]. Despite its potency, this agent has several potentially lethal disadvantages, such as "coronary steal" in patients with coronary disease, which can trigger acute myocardial infarction [42, 43]. In addition, it may increase intracranial pressure and decrease cerebral blood flow [44]. ICU monitoring with intra-arterial BP measurement is required [30]. Another concern is cyanide toxicity. Thiocyanate is a metabolite of nitroprusside. In the absence of adequate amounts of thiosulfate (required for metabolism of nitroprusside), cyanide levels can rise quickly [45]. To reduce the potential for toxicity, sodium nitroprusside should be used for no more than 24 hours and at an infusion rate no greater than 2 μg/kg/min in patients with normal renal and hepatic function [45]. It is contraindicated in patients with impaired kidney function or hereditary optic nerve atrophy (due to increased nerve ischemia). The current monitoring methods for cyanide toxicity are not sensitive, and while red blood cell (RBC) cyanide concentrations are more reliable, this test is not widely available. Patients with RBC cyanide concentration >40 nmol/mL have detectable metabolic changes and those with levels >200 nmol/L have clinical symptoms (coma,

encephalopathy, convulsion, irreversible focal neurologic abnormalities). Red blood cell cyanide concentration levels greater than 400 nmol/mL are considered lethal. For these reasons, sodium nitroprusside should be used only when no other intravenous (IV) antihypertensive agents are available.

Nitroglycerin This is a venodilator that decreases preload, increases coronary blood flow, inhibits coronary vasospasm, and decreases cardiac oxygen demands [46]. It can also cause arterial vasodilation, but not until high doses are reached. It is the preferred agent in emergencies complicated with ischemic heart disease, after a coronary bypass, or for the management of aortic dissection in conjunction with a β-blocker [47]. The recommended initial dose is 5 μg/kg/min, which can be increased 5 μg/kg/min every 3–5 minutes. After the dose reaches 20 μg/kg/min, it can be incrementally increased by 20 μg/kg/min. Nitroglycerin has no dosing limits (although the risk of hypotension is greater after 200 μg/kg/min). The onset of action is 2–5 minutes and the duration is 3–5 minutes. Adverse effects include tachyphylaxis (usually after four hours of IV infusion) and methemoglobinemia [48]. Volume status should be addressed before administration due to the possibility of reduced cardiac output and preload in the volume-depleted patient [49]. A common complaint of patients receiving nitroglycerin is headache.

Calcium Channel Blockers

While oral/sublingual nifedipine has been widely used, this drug has an unpredictable effect and is not recommended by the U.S. Food and Drug Administration (FDA) due to potential serious adverse effects [50].

Nicardipine This second-generation dihydropyridine has a high selectivity for coronary and cerebral vasodilator activity, increasing the blood flow in these organs [51]. The onset of action is 5–15 minutes, [52] and the duration is up to three hours [52, 53]. The initial infusion rate is 5 mg/hour, and the dose can be titrated up by 2.5 mg/hour every five minutes. The manufacturer recommends a maximum dose of 15 mg/hour. In the author's experience, doses as high as 30 mg/hour can be tolerated with minimal adverse effects [30]. The plasma concentration can increase over 24 hours, resulting in an unexpected prolonged time of action. Nicardipine is metabolized in the liver and is cleared renally. Blood pressure control is usually achieved in 10–15 minutes [54]. American Heart Association guidelines recommend this agent in acute ischemic stroke when SBP is >220 mmHg or DBP is >120 mmHg [55].

Nicardipine has been compared favorably to other first-line agents in several trials. In a study comparing IV nicardipine with sodium nitroprusside, Neutel and associates demonstrated that nicardipine provided a greater reduction in SBP and DBP and was more effective in patients with severe hypertension [56]. The CLUE trial, a randomized comparative effectiveness study of IV nicardipine versus labetalol use in the emergency department, revealed that nicardipine was more effective in reaching the SBP target within 30 minutes than labetalol [57••].

Clevidipine This third-generation dihydropyridine is metabolized by RBC esterases, and therefore its breakdown is not altered by renal or hepatic failure [12, 58]. A direct coronary vasodilator, clevidipine increases coronary blood flow while increasing stroke volume and cardiac output, protects against ischemia/reperfusion injury, and maintains splanchnic blood flow and renal function [57••].

Because of its metabolism, clevidipine has an ultrashort half-life of only 2–4 minutes [59••]. The initial rate of infusion is 0.4 μg/kg/min, and is titrated up by doubling increments every 90 seconds, to a maximum of 3.2 μg/kg/min [60]. The maximum 24-hour dosage should not exceed 2.5 g/kg [30, 61•]. Due to its lipid emulsion formulation, it is recommended that the infusion line be changed frequently to prevent potential bacterial contamination [62•]. Since the formulation includes soybean oil and purified egg yolk phospholipids, it should not be given to patients with egg or soy allergies.

Several comparative and single-agent trials have addressed the efficacy of clevidipine. The ESCAPE-1 (Efficacy Study of Clevidipine Assessing Its Preoperative Antihypertensive Effect in Cardiac Surgery-1) trial studied preoperative patients with SBP of ≥160 mmHg, and ESCAPE-2 studied postoperative patients with SBP of ≥140 mmHg [60, 63]. These investigations compared clevidipine in doses of 0.4 μg/kg/min, doubled every 90 seconds, to placebo, and demonstrated a lowering effect 1–2 minutes after infusion was initiated, with an average of 6 minutes and 5.3 minutes to reach target BP (15 % reduction) in preoperative and postoperative patients, respectively. The ECLIPSE (Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events) study compared clevidipine with nitroglycerin, sodium nitroprusside, and nicardipine [64•]. Overall, patients who received clevidipine had lower rates of mortality (2.8 % vs 3.8 %), fewer total adverse effects, and improved BP control compared to patients who received the other two agents [64•]. A subanalysis of the VELOCITY (Evaluation of the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients with Severe Hypertension) trial was performed to confirm the safety and efficacy of clevidipine in acute hypertension (SBP >180 mmHg) with acute heart failure. Patients received an initial dose of 2 mg/hour, titrated to double the dose every three minutes up to 32 mg/hour, with 88.9 % of patients reaching target BP within 30 minutes (median of 10.9 min) [65•]. The most common adverse effects observed were headache, nausea, chest discomfort, and vomiting. In addition, the trial documented successful transition to oral medications.

Sympathoplegic Agents

Labetalol This is a combined α1-adrenergic (selective) and β-adrenergic (non-selective) receptor blocker, with a seven-fold greater effect on the β receptors as compared to the α receptors [66]. Labetalol can be administered either as a bolus or continuous infusion [67, 68]. The onset of action is 2–5 minutes after administration, lasting 2–4 hours [69], with a half-life of 5.5 hours [70••]. Patients with good intravascular volume experience no reduction in cardiac output, and the heart rate is maintained or slightly reduced [71]. The recommended initial dosing is a load of 20 mg, followed either by boluses of 20–80 mg every 10 minutes (at the risk of hypotension) or titrated to a continuous infusion rate of 1–2 mg/min [72•]. The total maximum dose is 300 mg. The drug is commonly used in pregnancy because of its poor ability to cross the maternal-fetal barrier [73]. Contraindications due to its beta-blocker effect include pre-existing heart block, asthma, bradycardia, and severe congestive heart failure [71]. As noted above, this agent was compared to nicardipine in the CLUE trial [57••]. Labetalol may also be used for BP control *in conjunction* with a vasodilator in patients with hypertensive crisis due to cocaine [74••].

Esmolol This is an ultrashort-acting cardioselective beta -blocking agent, with onset of action within 60 seconds and duration of 10–20 minutes [75, 76]. Esmolol has been described as the "ideal" beta blocker agent for critically ill patients [77], as it reduces heart rate and myocardial contractility but has no vasodilatory effect [75]. Its metabolism by RBC esterases allows the medication to be safely used in patients with underlying renal or hepatic pathology [78]. Administration is usually a 0.5 mg/kg loading dose for 60 seconds, followed by continuous infusion, starting at 50 μg/kg/min, which can be titrated up to 300 μg/kg/min [79]. Contraindications for esmolol are due to its metabolic effects. For example, anemia may prolong its half-life (RBC esterases are reduced). The agent should also be avoided in patients who are already on a beta blocker, have bradycardia, or have heart failure exacerbation [80].

Alpha-1 Blockers

Phentolamine This is a pure α-adrenergic antagonist, agent of choice in the initial management of catecholamine-induced hypertensive emergencies [14]. The starting dose is 1–5 mg IV boluses, the onset of action is immediate, and half-life is 15 minutes [81, 82]. Phentolamine is only recommended for use as an initial agent (e.g., pheochromocytoma), as it may cause tachyarrhythmias or angina, and a longer-acting α -adrenergic antagonist like oral phenoxybenzamine should be administered once the crisis is under control [83].

Angiotensin-Converting Enzyme (ACE) Inhibitors

Enalaprilat This ACE inhibitor can be administered intravenously, at an initial dose of 1.25 mg over five minutes, over a period of 12–24 hours, with a maximum dose of 5 mg every six hours [30]. The onset of action is 15 minutes, with peak action in one hour. The half-life is 11 hours, but the normal duration of action is estimated to be six hours. Advantages of enalaprilat include the absence of reflex tachycardia and minimal to no effect on intracranial pressure [12]. Contraindications include patients with hyperkalemia, circulatory decompensation (due to the risk of acute renal failure), or whose mean arterial pressure is insufficient for adequate renal perfusion [84]. As with all ACE inhibitors, this agent is contraindicated in pregnancy.

Conclusions

Hypertensive emergencies are always critical conditions and must be swiftly addressed, with constant monitoring and care to prevent further target-organ damage. While there are a wide variety of pharmaceutical agents available, the mechanism of action and contraindications of each must guide the choice of treatment for optimal care. We favor titratable ultrashort-acting agents initially, followed by longer-acting oral agents once BP control is established and the patient is medically stable.

Compliance with Ethics Guidelines

Conflict of Interest Alan Padilla Ramos declares that he has no conflict of interest.

Joseph Varon is a consultant and part of the speaker's bureau for the Medicines Company, Baxter Pharmaceutical and Cornerstone Pharmaceutical.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension. 2008;52(5):818–27.
2. Vital signs: prevalence, treatment, and control of hypertension–United States, 1999-2002 and 2005-2008. Morb Mortal Wkly Rep. 2011;60(4):103-8.

3. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290(2):199–206.
4. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117(4):e25–e146.
5. Whitworth JA. 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens. 2003;21(11):1983–92.
6. Volhard F. Die Brightsche Nierenkrankheit: Springer; 1914.
7. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci. 1974;268(6):336–45.
8. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension. 2003;41(6):1178–9.
9.• James PA, Oparil S, Carter BL, et al. evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20. *This latest report of the JNC offers classes of medications that can be used for BP control. Although this review does not adress the hypertensive crisis, it is one of the most important references in the United States and throughout the world for treating this pathology.*
10. Varon J, Marik PE. The diagnosis and management of hypertensive crises. Chest. 2000;118(1):214–27.
11. Varon J. Treatment of acute severe hypertension: current and newer agents. Drugs. 2008;68(3):283–97.
12. Varon J. Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises. Am J Emerg Med. 2007;25(8):949–59.
13. Schiller JS, Lucas JW, Ward BW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey, 2010. Vital and health statistics Series 10, Data from the National Health Survey. 2012(252):1-207
14. Prisant LM, Carr AA, Hawkins DW. Treating hypertensive emergencies. Controlled reduction of blood pressure and protection of target organs. Postgrad Med. 1993;93(2):92–6. *101-4, 8-10.*
15. Marik PE, Varon J. Hypertensive crises: challenges and management. Chest. 2007;131(6):1949–62.
16. Varon J, Marik P. Clinical review: the management of hypertensive crises. Crit Care. 2003;7(5):374–84.
17. Ault MJ, Ellrodt AG. Pathophysiological events leading to the end-organ effects of acute hypertension. Am J Emerg Med. 1985;3(6 Suppl):10–5.
18. Wallach R, Karp RB, Reves JG, Oparil S, Smith LR, James TN. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol. 1980;46(4):559–65.
19. Han Y, Runge MS, Brasier AR. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa B transcription factors. Circ Res. 1999;84(6):695–703.
20. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies. Prevalence and clinical presentation. Hypertension. 1996;27(1):144–7.
21. Garcia Jr JY, Vidt DG. Current management of hypertensive emergencies. Drugs. 1987;34(2):263–78.
22. Finnerty Jr FA. Management of hypertensive encephalopathy. Herz. 1978;3(5):300–4.
23. Chen K, Varon J, Wenker OC, Judge DK, Fromm Jr RE, Sternbach GL. Acute thoracic aortic dissection: the basics. J Emerg Med. 1997;15(6):859–67.
24. Khan IA, Nair CK. Clinical, diagnostic, and management perspectives of aortic dissection. Chest. 2002;122(1):311–28.
25. Estrera AL, Miller 3rd CC, Safi HJ, et al. Outcomes of medical management of acute type B aortic dissection. Circulation. 2006;114(1 Suppl):I384–9.
26. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet. 2000;356(9227):411–7.
27. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17–22.
28. Weder AB, Erickson S. Treatment of hypertension in the inpatient setting: use of intravenous labetalol and hydralazine. J Clin Hypertens. 2010;12(1):29–33.
29.•• Fontes ML, Varon J. Perioperative hypertensive crisis: newer concepts. Int Anesthesiol Clin. 2012;50(2):40–58. *Over 72 million of Americans have hypertension. Of the patients that present to non-cardiac surgery one third are hypertensive. The consequences of hypertension are been associated with multiple target-organ complications. This article provides an overview of hypertensive crises.*
30. Varon J, Marik PE. Perioperative hypertension management. Vasc Health Risk. 2008;4(3):615–27.
31.• Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–65. *This study randomly assigned patients with spontaneous intracerebral hemorrhage to receive therapy to lower systolic blood pressure to either <180mmHg (guideline-recommended) or <140mmHg. Subjects demostrated improved functional outcomes with intensive SBP lowering treatment.*
32.• Hill MD, Muir KW. INTERACT-2: should blood pressure be aggressively lowered acutely after intracerebral hemorrhage? Stroke. 2013;44(10):2951–2. *This study randomly assigned patients with spontaneous intracerebral hemorrhage to receive therapy to lower systolic blood pressure to either <180mmHg (guideline-recommended) or <140mmHg. They demostrated that <140mmHg is a safe target and suggested that additional data is required to recommend this practice.*
33.• Sarafidis PA, Georgianos PI, Malindretos P, Liakopoulos V. Pharmacological management of hypertensive emergencies and urgencies: focus on newer agents. Expert Opin Investig Drugs. 2012;21(8):1089–106. *In this review the author suggests the use of less toxic hypertensive agents like nicardipine, fenoldopam, labetalol and esmolol over older agents such as nitroprusside, nitroglycerin and hydralaizne.*
34. Schirger A, Spittell Jr JA. Pharmacology and clinical use of hydralazine in the treatment of diastolic hypertension. Am J Cardiol. 1962;9:854–9.
35. Cogan JJ, Humphreys MH, Carlson CJ, Rapaport E. Renal effects of nitroprusside and hydralazine in patients with congestive heart failure. Circulation. 1980;61(2):316–23.
36. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003;327(7421):955–60.
37. 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(6):653–62.
38. Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. Circulation. 1990;81(3):970–7.
39. Reisin E, Huth MM, Nguyen BP, Weed SG, Gonzalez FM. Intravenous fenoldopam versus sodium nitroprusside in patients with severe hypertension. Hypertension. 1990;15(2 Suppl):I59–62.
40. Duprez D. Arterial Hypertension. In: Toth PP, Cannon CP, editors. Comprehensive Cardiovascular Medicine in the Primary Care Setting: Humana Press; 2011. p. 25-58.

41. Friederich JA, Butterworth JF. Sodium nitroprusside: twenty years and counting. Anesth Analg. 1995;81(1):152–62.
42. 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(19):1129–35.
43. Mann T, Cohn PF, Holman LB, Green LH, Markis JE, Phillips DA. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease. Results in 25 patients and comparison with nitroglycerin. Circulation. 1978;57(4):732–8.
44. Griswold WR, Reznik V, Mendoza SA. Nitroprusside-induced intracranial hypertension. JAMA. 1981;246(23):2679–80.
45. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. Am J Crit Care. 1992;1(2):19–25.
46. Parent R, Leblanc N, Lavallee M. Nitroglycerin reduces myocardial oxygen consumption during exercise despite vascular tolerance. Am J Physiol Heart Circ Physiol. 2006;290(3):H1226–34.
47. Flaherty JT, Magee PA, Gardner TL, Potter A, MacAllister NP. Comparison of intravenous nitroglycerin and sodium nitroprusside for treatment of acute hypertension developing after coronary artery bypass surgery. Circulation. 1982;65(6):1072–7.
48. Brundtland GH. From the World Health Organization. Reducing risks to health, promoting healthy life. JAMA. 2002;288(16):1974.
49. Toman J, Lupinek Z, Janousek S, Nechvatal L, Zeman K. Hemodynamic effects of transdermal nitroglycerin patches in patients with acute myocardial infarction. Cardiology. 1991;79 Suppl 2:58–62.
50. Levy JH. Treatment of perioperative hypertension. Anesthsiol Clin of N Am. 1999;17(3):567–79.
51. Munoz Alameda LE, Barcina Sanchez M. [Intravenous nicardipine: a new calcium antagonist for perioperative use. Rev Esp Anestesiol Reanim. 2001;48(2):71–80.
52. Wallin JD, Cook ME, Blanski L, et al. Intravenous nicardipine for the treatment of severe hypertension. Am J Med. 1988;85(3):331–8.
53. Sorkin E, Clissold S. Nicardipine. Drugs. 1987;33(4):296–345.
54. Kross RA, Ferri E, Leung D, et al. A comparative study between a calcium channel blocker (Nicardipine) and a combined alpha-beta-blocker (Labetalol) for the control of emergence hypertension during craniotomy for tumor surgery. Anesth Analg. 2000;91(4):904–9.
55. Drozda Jr J, Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. J Am Coll Cardiol. 2011;58(3):316–36.
56. Neutel JM, Smith DH, Wallin D, et al. A comparison of intravenous nicardipine and sodium nitroprusside in the immediate treatment of severe hypertension. Am J Hypertens. 1994;7(7 Pt 1):623–8.
57.•• Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. Crit Care. 2011;15(3):R157. *This was a multicenter randomized clnical trial with the objective of comparing IV nicardipine versus IV labetalol using doses recommended by the food and drug administration. A total of 226 patients were enrolled. Nicardipine-receiving patient reached BP goals more often than labetalol-receiving patients 30 minutes after the dose. No significant diference in adverse effects was noted*.
58. Rivera A, Montoya E, Varon J. Intravenous clevidipine for management of hypertension. Integr Blood Press Control. 2010;3:105–11.
59.•• Espina IM, Varon J. Clevidipine : a state-of-the-art antihypertensive drug under the scope. Expert Opin Pharmacother. 2012;13(3):387–93. *This article analyzed the characteristics of Clevidipine including half-life, interaction, dosings and efficacy. Over 90% of patients receiving clevidipine reached target blood pressure within 30 minutes of administration*.
60. Levy JH, Mancao MY, Gitter R, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. Anesth Analg. 2007;105(4):918–25.
61.• Tulman DB, Stawicki SP, Papadimos TJ, Murphy CV, Bergese SD. Advances in management of acute hypertension: a concise review. Disc Med. 2012;13(72):375–83. *This review focuses on Clevdipine as an effective hypotensive agents, focusing on the pharmacodynamic and pharmacokinect properties and the saftly profile*.
62.• Mirtallo JM, Dasta JF, Kleinschmidt KC, Varon J. State of the art review: Intravenous fat emulsions: current applications, safety profile, and clinical implications. Ann Pharmacother. 2010;44(4):688–700. *This review focuses on propofol and clevidipine to assess the safety profile of intravenous fat emulsions, demonstrating a low rate of lipid-related adverse effects when administrered within guideline recommendations*.
63. Singla N, Warltier DC, Gandhi SD, et al. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg. 2008;107(1):59–67.
64.• Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008;107(4):1110–21. *Data from three prospective studies demostrate that there was no difference in the incidence of adverse effects between clevidipine-receiving patients compared with the other hypotensive drugs*.
65.• Peacock F, Varon J, Ebrahimi R, Dunbar L, Pollack Jr CV. Clevidipine for severe hypertension in acute heart failure: a VELOCITY trial analysis. Congest Heart Fail. 2010;16(2):55–9. *In patients with acute heart failure, there were no treatment-related adverse effects, demostrating that clevidipine is a safe agent to decrease SBP in this group of patients*.
66. Conner CS. Labetalol: an alpha- and beta-blocker. Drug Intell Clin Pharm. 1983;17(7–8):543–4.
67. Huey J, Thomas JP, Hendricks DR, Wehmeyer AE, Johns LJ, MacCosbe PE. Clinical evaluation of intravenous labetalol for the treatment of hypertensive urgency. Am J Hypertens. 1988;1(3 Pt 3):284s–9s.
68. Wright JT, Wilson DJ, Goodman RP, Minisi AJ. Labetalol by continuous intravenous infusion in severe hypertension. J Clin Hypertens. 1986;2(1):39–43.
69. Richards DA. Pharmacological effects of labetalol in man. Brit J Clin Pharmacol. 1976;3(4 Suppl 3):721–3.
70.•• Cannon CM, Levy P, Baumann BM, et al. Intravenous nicardipine and labetalol use in hypertensive patients with signs or symptoms suggestive of end-organ damage in the emergency department: a subgroup analysis of the CLUE trial. BMJ open. 2013;3(3). *The objective of this study was to compare IV infusion of nicardipine vs IV bolus of labetalol to manage hypertensive emergencies. Of the 141 patients who were enrolled, 49.6% received nicardipine and 51.7% received labetalol. Patients receiving nicardipine were statisticaly more likely to reach target SBP within 30 minutes than those who received labetalol.*
71. MacCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. Pharmacotherapy. 1983;3(4):193–219.
72.• Shekhar S, Sharma C, Thakur S, Verma S. Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol. 2013;122(5):1057–

63. *This trial pregant women with SBP >159mmHg or DPB >109mmHg received 10mg of nifedipine PO, 20,40,80mg of labetalol or IVor placebo. Nifedipinelowered blood pressure more quickly than labetalol.*
73. Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V. Hypertension crisis. Blood Press. 2010;19(6): 328–36.
74.•• Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/ non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1–e157. *This ACC/AHA Guidelines defined systolic hypertension as a predictor of adverse outcome in UA/NSTEMI, and recommend medical management and lifestyle changes*.
75. Gray RJ. An ultra short-acting beta-adrenergic blocker. Chest. 1988;93(2):398–403.
76. Rosei EA, Trust PM, Brown JJ, Lever AF, Robertson JI. Letter: intravenous labetalol in severe hypertension. Lancet. 1975;2(7944): 1093–4.
77. Turlapaty P, Laddu A, Murthy VS, Singh B, Lee R. Esmolol: a titratable short-acting intravenous beta blocker for acute critical care settings. Am Heart J. 1987;114(4 Pt 1):866–85.
78. Esmolol WD. A review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharmacokinet. 1995;28(3):190–202.
79. Varon J. The diagnosis and treatment of hypertensive crises. Postgrad Med. 2009;121(1):5–13.
80. Zangrillo A, Turi S, Crescenzi G, et al. Esmolol reduces perioperative ischemia in cardiac surgery: a meta-analysis of randomized controlled studies. J Cardiothorac Vasc Anesth. 2009;23(5):625–32.
81. Ziegler MG. Advances in the acute therapy of hypertension. Crit Care Med. 1992;20(12):1630–1.
82. McMillian WD, Trombley BJ, Charash WE, Christian RC. Phentolamine continuous infusion in a patient with pheochromocytoma. Am J Health Syst Pharm. 2011;68(2):130–4.
83. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 2. Am J Health Syst Pharm. 2009;66(16): 1448–57.
84. Curry SC, Arnold-Capell P. Toxic effects of drugs used in the ICU. Nitroprusside, nitroglycerin, and angiotensin-converting enzyme inhibitors. Crit Care Clin. 1991;7(3):555–81.