Revista da SOCESP
Sociedade de Cardiologia do Estado de São Paulo

HYPERTENSIVE CRISES: DEFINING THE SEVERITY AND TREATMENT

CRISES HIPERTENSIVAS: DEFININDO A GRAVIDADE E O TRATAMENTO

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Received on 07/28/2018,
Accepted on 08/29/2018

ABSTRACT

The clinical conditions of an acute rise in blood pressure (BP) that characterize hypertensive crises are common in clinical practice, particularly in consultations that take place in the emergency room. Therefore the correct diagnosis is important for the best treatment and clinical outcome. Hypertensive crisis is defined as a sudden rise in BP (≥ 180/120 mmHg), and the need for aggressive reduction of BP depends on the severity of the associated clinical situation. The presence of new or progressive target organ injury and imminent risk of death define hypertensive emergencies requiring immediate treatment aimed at rapid reduction of blood pressure, not necessarily to normal levels. In most cases, the speed of the rise in BP is more important than the actual level of BP, and clinical evaluation is essential for the accurate diagnosis of these clinical conditions, which include hypertensive encephalopathy, acute coronary syndromes, pulmonary edema, stroke, aortic dissection, and eclampsia. The goals of BP reduction for hypertensive emergencies, according to the target organ involved, have been reviewed by the current Brazilian and American guidelines on hypertension. Treatment of hypertensive emergencies includes direct action vasodilators and adrenergic blockers, which are already well established, but recent evidence shows the benefit of the use of new drugs, not yet available in Brazil.

Keywords: Arterial Hypertension; Target Organs; Emergency Treatment.

RESUMO

As situações clínicas de aumento súbito da pressão arterial (PA) que caracterizam as crises hipertensivas são comuns na prática clínica, principalmente nas consultas realizadas no pronto atendimento, portanto, o diagnóstico adequado é essencial para o melhor tratamento e desfecho clínico. A crise hipertensiva é definida pelo aumento súbito na PA (≥180 /120 mmHg) e a necessidade da redução agressiva da PA depende da gravidade da situação clinica associada. A presença de lesões novas ou progressivas em órgãos-alvo e risco iminente de morte definem as emergências hipertensivas que requerem tratamento imediato visando a rápida redução da pressão arterial, porém, não, necessariamente, a níveis normais. Na maioria dos casos, a velocidade do aumento da PA é mais importante que o nível real da PA, portanto, é fundamental que haja avaliação clínica para o diagnóstico preciso dessas condições clínicas, as quais incluem encefalopatia hipertensiva, síndromes coronarianas agudas, edema agudo dos pulmões, acidente vascular cerebral, dissecção de aorta e eclampsia. As metas para diminuição da PA para as emergências hipertensivas, de acordo com o órgão-alvo envolvido, são revisadas pelas atuais diretrizes brasileiras e americanas de hipertensão. O tratamento das emergências hipertensivas inclui vasodilatadores de ação direta e bloqueadores adrenérgicos já consagrados, entretanto, evidências recentes mostram o benefício do uso de novos fármacos ainda não disponíveis em nosso meio.

Descritores: *Hipertensão Arterial; Órgãos-Alvo; Tratamento de Emergência.*

INTRODUCTION

Systemic arterial hypertension (SAH) affects 31.1% of the world's adult population and is recognized as the main risk factor for the development of cardiovascular diseases and cardiovascular death.[1] In Brazil, approximately one third of the adult population has SAH, which is one of the main causes of hospital admission.[2]

Acute or chronic blood pressure (BP) elevations are very common in clinical practice, and an accurate diagnosis is of utmost importance for its better treatment and, consequently, clinical outcome. Among the clinical situations that occur with acute BP elevation, hypertensive crisis (HC) stands out. It is defined as sudden increases in BP, i.e., systolic BP (SBP) of ≥180 mmHg and diastolic BP (DBP) of ≥120 mmHg, which

may or may not result in target organ damage (TOD; heart, brain, kidneys, and arteries).[3-7] HC can occur in two distinct ways varying with respect to severity and prognosis. Hypertensive emergency (HE) presents as a marked increase in BP associated with TOD and immediate risk of death, a fact that requires a rapid and gradual reduction of tension levels in minutes to hours, with intensive monitoring and use of intravenous drugs.[3-7] It may manifest itself as a cardiovascular, cerebrovascular, renal, or gestational event, in the form of pre-eclampsia or eclampsia. Although the BP at presentation is often very high (≥180/120 mmHg), it is not the degree of BP elevation, but rather the patient's clinical status that defines the emergency. For example, a previously non-hypertensive individual with nephritic syndrome, a 60-year-old man with a BP of 160/110 mmHg and acute aortic dissection, or even a woman in the third trimester of pregnancy with eclampsia and slightly elevated BP (150/95 mmHg) are examples of true hypertensive emergencies (HE).[3-7] Therefore, the numerical definition of HC is conceptual and serves as a conduct parameter, but it should not be used as an absolute criterion. Table 1 shows the main clinical presentations of HE.

Conversely, hypertensive urgency (HU) is characterized by BP elevations, with no lesions in TOD and no risk of imminent death, a fact that allows slower reduction of BP in a period of 24 to 48 hours.[3-7] Currently, there is a wide discussion on the actual existence of the diagnosis "HU." Many advocate that this classification needs to be updated (if not abandoned) and that the greatest diagnostic importance should be centered on the presence of signs/symptoms and acute dysfunction of target organs, rather than on the value of BP. Others believe that the correct term should be "BP elevation without evolving TOD."[7] This questioning comes from the results of prospective clinical studies in which acute BP reduction did not show any direct benefit; further, the occurrence of adverse events was minimal, and the death rates were low in treated subjects compared with untreated subjects, indicating that there was no impairment in the group where BP was not rapidly reduced.[8,9] This was demonstrated by Levy et al.[8] who evaluated 435 patients with very high BP, but without TOD, treated with oral antihypertensive therapy in the emergency department and compared them with 581 similar patients who were not treated with antihypertensive drugs. Another study[9] retrospectively investigated 58,535 patients with HU who were followed up for 6 months after initial care and found that the rate of major cardiovascular events was very low and that most patients still had uncontrolled BP after 6 months of follow-up. In these cases, emergency care should include initial care, guidance on the importance of chronic treatment, and referral to follow-up in the public primary care network in a period ranging from a few days to a week.[10,11] However, two prospective studies have shown controversial results.[12,13] In one of these studies, Lee et al.[12] demonstrated that a "non-critical" hypertensive event seen in the emergency room was associated with a significantly increased risk of major cardiovascular events during a follow-up period of up to 10 years. In the other study, the authors reported that HU was independently associated with cardiovascular events during the follow-up period (median, 4.2 years).[13] Therefore, regardless of initial care, it is important to follow these patients up and to control their BP over time, since individuals who present HU are exposed to a greater risk of future cardiovascular events compared with individuals with hypertension who do not present this complication. Thus, we can conclude that the rapid reduction of BP in these situations is not justified; however, the control of BP in the medium and long term will be beneficial for cardiovascular disease prevention.

Table 1. Main clinical presentations of hypertensive emergency.

Cerebrovascular lesions	Hypertensive encephalopathy
	Ischemic stroke
	Hemorrhagic stroke
	Subarachnoid hemorrhage
Cardiovascular lesions	Acute coronary syndrome (acute myocardial infarction/unstable angina)
	Acute pulmonary edema
	Acute aortic dissection
Kidney lesions	Rapidly progressive renal failure
Pregnancy	Pre-eclampsia/eclampsia
Catecholaminergic crises	Pheochromocytoma crisis
	Overdose with sympathomimetic drugs (lysergic acid diethylamide, cocaine, and phenylpropanolamine)
	Rebound hypertension after withdrawal of antihypertensive drugs (clonidine or beta-blockers)
	Interaction of tyramine with monoamine oxidase inhibitors
Other presentations	Brain trauma

Other situations also occur with BP elevation and are part of the differential diagnosis of HC; these include hypertensive pseudocrisis (HP), resistant hypertension, and malignant hypertension. HP is a common condition in emergency care, a fact observed in 64.5% of patients with HC who actually had HP.[14] It is characterized by BP elevation without TOD and without immediate risk of death, much resembling that of HU. Generally, it occurs in patients with treated and uncontrolled hypertension or in those with untreated hypertension (uncomplicated severe chronic hypertension) referred to the hospital emergency department because they have a very high BP, but are oligosymptomatic or asymptomatic, highlighting the absence of TOD and immediate risk of death. Thus, it is important to emphasize the need for early outpatient follow-up after initial care. Another group of individuals with hypertension may present transient BP elevation in the presence of some emotional or painful event or some discomfort, such as migraine, rotatory vertigo, musculoskeletal vascular headache, and panic syndrome manifestations, which also characterize HP.[4] Resistant hypertension is another clinical condition included in the differential diagnosis of HC.[4-7] In resistant SAH, there is no evidence of acute TOD or indication of rapid BP reduction, a situation similar to that found in HP and HU. The physician's therapeutic decision should be based more on clinical assessment findings and the presence of acute lesions than on BP. Finally, malignant hypertension and accelerated hypertension

are terms that are used interchangeably to describe a scenario that presents severe hypertension with rapidly progressive TOD (mainly renal failure, severe left ventricular hypertrophy, severe retinopathy with exudates, and retinal hemorrhages with or without papilledema) and fatal clinical outcomes.[15]

Currently, the term HE is used to refer to elevated BP complicated with acute TOD.

EPIDEMIOLOGY OF HC

It is estimated that true HC affects nearly 1% of the population with hypertension (in Brazil, there are more than 360,000 patients with hypertension affected), illustrating the importance of correct diagnosis and treatment of this condition.[3-7] HC accounts for a variable rate of 0.45% to 0.59% of all hospital emergency room visits and 1.7% of clinical emergencies, with HU being more common than HE. Ischemic stroke and acute pulmonary edema are the most frequent conditions in HE.[16-18]

PHYSIOPATHOGENESIS

The precise physiopathogenesis of HE is poorly understood. However, two different but interrelated mechanisms may play central roles in their physiopathogenesis. The first mechanism is the failure of the vascular bed self-regulation system, which occurs with a reduction in perfusion pressure, with consequent decreased blood flow and increased vascular resistance, resulting in mechanical stress and endothelial injury.[19] The second mechanism is the activation of the renin-angiotensin system, leading to greater vasoconstriction, generating a vicious cycle of injury and subsequent ischemia.[20] In addition to these mechanisms, a prothrombotic state may play a fundamental role in HE.[21]

The initial clinical evaluation should include directed anamnesis and objective physical examination, focusing on the target organ affected by the acute BP elevation.[22] Patients with a higher risk of death should be treated as soon as possible, and a complete medical history should be obtained later.

The important data that should be obtained from patients include the following: duration of history of hypertension, BP before the event, symptoms related to TOD (e.g., chest pain, dyspnea, headache, syncope, and motor or visual deficits), use of drugs with possible effects of BP elevation (e.g., anti-inflammatory, immunosuppressive, corticosteroid, and sympathomimetic drugs), use of illicit drugs (e.g., cocaine), history of obstructive sleep apnea syndrome, presence of other cardiovascular risk factors and other comorbidities, and symptoms that suggest a secondary cause of hypertension (e.g., pheochromocytoma, primary hyperaldosteronism, and renal artery stenosis).[20]

Physical examination should be objective, with a focus on adequate measurement of BP and assessment of signs of target organ decompensation. Thus, BP should be measured in both upper limbs, with the patients in the supine position and, if possible, in the orthostatic position; the peripheral pulses should be palpated, aiming at the detection of asymmetry or absence of such; the heart and respiratory rates should be measured, in addition to the oxygen saturation;[20] and cardiac auscultation helps evaluate the presence of murmurs, whereas lung auscultation is important for the detection of pulmonary congestion. Careful neurological examination and fundoscopy to evaluate the retina are also mandatory in patients with suspected HC.

Table 2 shows the main symptoms and signs and findings of complementary examinations of TOD important for the diagnosis of HC.

The frequency of signs and symptoms in HC varies according to the population studied. In a Brazilian study[16] conducted in a reference hospital, the most frequent symptoms were headache (44.3%), vertigo (29.3%), dyspnea (16.5%), and neurological deficit (15.7%); in an Italian study,[23] the most frequent findings were headache (17%), chest pain (13%), and epistaxis (13%). The differences between these studies can be attributed to the differences in the age group, since the Brazilian study investigated younger individuals.

TREATMENT

HE

There is no evidence based on randomized clinical studies that antihypertensive drugs reduce the morbidity and mortality in patients with HE; however, from clinical experience with these severe complications, benefits from antihypertensive therapy are highly likely and intuitive.[24]

For the treatment of HE, it is very important to consider the precise diagnosis of the type of emergency and the pharmacological characteristics of the drugs to be used, such as the main mechanism of action, time of action, side effects, and contraindications. These aspects are important in defining pressure reduction goals and the best therapeutic option.

Regarding BP control, BP monitoring should be rigorous, i.e., performed every 5 to 10 minutes with automatic measurements or, if possible, with an intra-arterial invasive measurement. The recent American hypertension guidelines[3] recommend intensive care unit admission of adults with HE for continuous monitoring of BP and TOD and administration of appropriate parenteral agents.

BP reduction should be programmed, considering that BP normalization is not necessary, but a rapid reduction, with a general reduction goal of $\leq$25% in the first hour to a BP of 160/100-110 mmHg in 2 to 6 hours, reaching values near 135/85 mmHg in 24 to 48 hours.[3,5]

The goals of BP reduction are different according to the type of HE in terms of the rate of reduction and in relation to the values to be reached (Table 3). Cardiovascular emergencies should be corrected more rapidly, especially aortic dissection, where normalization of BP should be achieved as soon as possible, because the mortality due to this complication is very high and directly related to BP. In this regard, the US guidelines[3] recommend that the SBP should be reduced to $<$140 mmHg during the first hour in cases of severe preeclampsia, eclampsia, or pheochromocytoma crisis and $<$120 mmHg in case of aortic dissection. In neurological emergencies, we should reduce the BP more carefully, without dramatically doing so in the first hours and with normalization being recommended only after 24 to 48 hours.

There is also no high-quality evidence to guide clinicians and intensivists on which first-line antihypertensive drug promotes more benefit than damage in the treatment of HE.

Thus, for the control of HE, the selection of the antihypertensive agent should be based on the pharmacology of the drug, pathophysiological factors related to the type of

Table 2. Relevant findings of anamnesis, physical examination, and complementary tests for the diagnosis of hypertensive emergencies and urgencies

Target organ	Symptoms	Physical examination	Complementary tests
Heart	Dyspnea, orthopnea, hemoptoic sputum, precordial or retrosternal pain, edema, or palpitations	3rd or 4th sound, pulmonary crackles, edema, jugular stasis, deviation of the ictus, or hepatomegaly	ECG: chamber overload, signs of ischemia (ST segment and T wave), or arrhythmias Chest x-ray: increased cardiac area or pulmonary congestion Echocardiogram: ventricular hypertrophy, atrial enlargement, or systolic and diastolic ventricular dysfunction
Kidney	Edema, oliguria, anorexia, weight loss, nausea, vomiting, or adynamia	Skin paleness, uremic fetor, or periorbital and lower limb edema	Elevated levels of urea and creatinine, proteinuria, hematuria, or anemia Renal ultrasound: changes in the renal parenchyma
Brain	Headache, mental confusion, psychomotor agitation, motor deficit, paresthesia, seizure, or nausea	Changes in the level of consciousness, paresis or paralysis of the limbs, rhyme deviation, anisocoria, reflex changes, or signs of meningeal irritation	Brain tomography: hemorrhage, infarction, or edema Resonance: infarction or specific changes
Retina	Blurring or blurred vision, phosphenes, scotoma, or amaurosis	Fundoscopy: cotton-wool exudates, retinal hemorrhages, or papilledema	
Aorta	Severe chest pain, back pain, or low back pain	Asymmetry or absence of peripheral pulses; Blood pressure difference between the limbs	Transesophageal echocardiogram: signs of dissection and valve insufficiency Angiotomography: level and extent of dissection

Table 3. Goals for the reduction of BP in major hypertensive emergencies.

Hypertensive emergency	Goals
General	- Reduction of ≤25% of the BP in the first hour
	- Achieving a BP of 160/100-110 mmHg in 2-6 h
Heart and aorta	
Acute pulmonary edema	- Reduction of ~10-15% in the MAP in 30-60 min
Myocardial ischemia	- Reduction of ~10-15% in the MAP in 30-60 min
Aortic dissection	- Reduction to 120/80 mmHg in 20 min
Brain	
Hypertensive encephalopathy	- BP=160-180/100-110 mmHg in 2-3 h.
Hemorrhagic stroke	- If the SBP is 150-220 mmHg with no contraindication to treatment: acute reduction of the SBP to 140 mmHg
	- If the SBP is >220 mmHg: aggressive BP reduction with continuous intravenous infusion and frequent BP monitoring
Subarachnoid hemorrhage	- Reduction of the BP to 170-180/100 mmHg in 6-12 h
Ischemic stroke	- If the initial BP is >220/120 mmHg with no indication for thrombolytic therapy: BP reduction of up to 15-20%, with DBP remaining at 100-110 mmHg in 24 h

hypertension, severity of the progression of TOD, desired speed of BP reduction, and presence of comorbidities.[3] Furthermore, because tissue self-regulation is impaired in HE, continuous infusion of titratable short-acting antihypertensive drugs is often preferable to prevent further TOD.[25]

Therefore, the recommended[5] drugs are those that can be used parenterally (intravenous) with rapid onset and easy titration, in which direct action vasodilators and adrenergic blockers stand out (Table 4). Among these drugs, sodium nitroprusside may be indicated for most patients with HE; however, depending on the clinical situation, there are more benefits when BP is reduced using other more specific therapeutic classes.

It is also important to consider practical questions because if the best therapeutic option is not available for the treatment of HE, preference should be given to the most similar drug possible aimed at controlling BP.

Sodium nitroprusside acts by spontaneously releasing nitric oxide, which activates guanyl cyclase, increasing the level of cyclic GMP, which promotes the dephosphorylation of myosin light chain phosphatase, with consequent relaxation of the vascular smooth muscle, generating arterial and venous vasodilation. It has a rapid onset of action and a short half-life, allowing a reduction of BP within minutes.[5,15] The most common side effects, when used in high doses and for a longer period, are nausea, vomiting, convulsion, and mental confusion.[15]

Nitroglycerin, another vasodilator for parenteral use, has a predominantly venous action, leading to a significant reduction in ventricular preload and afterload, and is the most indicated drug in HE related to acute coronary syndrome.[5,15] It is also indicated in the treatment of acute pulmonary edema as an alternative to sodium nitroprusside. The most commonly

Table 4. Drugs indicated for the treatment of hypertensive emergencies available in Brazil (adapted from the VII Brazilian Guidelines on Hypertension, 2016).

Drugs	Class	Dose	Onset of action	Duration of action	Indications
Sodium nitroprusside	Arterial and venous vasodilator (stimulates formation of cyclic GMP).	0.25-10 µg/kg/min continuous IV infusion	Immediate	1-2 min	Most hypertensive emergencies
Nitroglycerin	Arterial and venous vasodilator, nitric oxide donor	5-15 mg/h continuous IV infusion	2-5 min	3-5 min	Coronary insufficiency, left ventricular failure with APE
Hydralazine	Direct-acting vasodilator	10-20 mg IV or 10-40 mg IM 6/6 h	10-20 min IV 20-30 min IM	3-12 hs	Eclampsia or imminent eclampsia
Esmolol	Ultra-fast-acting selective beta-blocker	Loading: 500 µg/kg Intermittent infusion: 25-50 µg/kg/min ↑25 µg/kg/min every 10-20 min Maximum: 300 µg/kg/min	1-2 min	1-20 min	Acute aortic dissection (in combination with SNP), severe postoperative hypertension
Furosemide	Loop diuretic	20-60 mg EV	2-5 min	30-90 min	Left ventricular failure with APE, hypervolemia
Metoprolol	Selective beta-blocker	5 mg IV (repeat 10/10 min, if necessary up to 20 mg)	5-10 min	3-4 h	Coronary insufficiency, acute aortic dissection (in combination with SNP)

observed adverse effects with high doses are headache, reflex tachycardia, flushing, and methemoglobinemia.

The other vasodilator used in HE is intravenous or intramuscular hydralazine, indicated mainly in eclampsia or imminence of eclampsia.[5,15] Its side effects include tachycardia, headache, vomiting, and worsening of angina and the infarction area; it is not indicated in cases of acute coronary syndrome. Caution is also needed in patients with elevated intracranial pressure.

Among adrenergic blockers, beta-blockers are the most commonly used, especially in acute coronary syndrome and aortic dissection.[5,15] In unstable angina or acute myocardial infarction, they are usually used in combination with nitroglycerin, reducing oxygen consumption by the ischemic myocardium. Another important indication of beta-blockers is acute aortic dissection where, in combination with sodium nitroprusside, they decrease the tension in the aortic wall and consequently attenuate the progression of aortic wall delamination.[15] Bradycardia, advanced atrioventricular block, and bronchospasm are the most frequently related adverse events.

Other adrenergic blockers indicated in adrenergic attacks (e.g., pheochromocytoma crisis), such as labetalol and phentolamine, are not available for use in Brazil.[3] Thus, in our setting, sodium nitroprusside is indicated initially, and later, oral alpha blockers are used until adequate BP control is achieved.[15] In cases of severe tachycardia, beta-blockers can be administered.

Other drugs not available in Brazil are indicated for HE.[3] Fenoldopam, a peripheral dopaminergic receptor agonist that promotes renal vasodilation, is recommended for raising BP associated with acute kidney injury.[3] Nicardipine, an intravenous fast-acting calcium channel blocker, is used to control BP in stroke and hypertensive encephalopathy,[3] and there is evidence that it is superior to labetalol in controlling BP in the short term.[26]

More recently, the new intravenous ultra-fast-acting calcium blocker, clevidipine, has been recommended by the guidelines for the treatment of neurological HE, including ischemic stroke and cerebral hemorrhage.[27] The current evidence demonstrates the efficacy of clevidipine in other HE, such as acute aortic dissection[28] and acute perioperative BP elevation.[29]

HU

HE should be therapeutically managed with oral antihypertensive agents that have relatively short onset of action and duration of action (1 to 6 hours).[5] In general, patients may be observed for some hours in a calm environment, with the objective of reducing BP and controlling symptoms. When clinical conditions are stable, patients can be discharged and should return for medical examination within 72 hours.

The most commonly used drugs for the treatment of HU in Brazil are clonidine (0.1-0.2 mg P.O. + 0.1-0.6 mg/h) and captopril (25 mg P.O. + 25 mg after 2 h).[15]

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: Each author contributed individually and significantly to the development of the manuscript. LAB, JVS, and JFVM performed the bibliographic search, reviewed the manuscript, and contributed to the study's intellectual concept.

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