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Editorial
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Hypertensive emergencies: still an emergency?

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Abstract

Patients with an acute increase in blood pressure, often described as hypertensive crises, remain a worldwide burden despite the advances in antihypertensive medication in the past century. The presence or absence of hypertension-mediated organ damage divides patients into hypertensive emergencies and hypertensive urgencies, respectively, requiring a more urgent approach for the management of hypertensive emergencies. Few data have been published regarding patients' long-term monitoring after the presenting episode. Therefore, further research is needed concerning the management and follow-up of these patients.

Keywords: hypertensive emergencies, diagnosis, treatment.

Definition

The term "hypertensive crisis" used so far has been replaced by "hypertensive urgency" and "hypertensive emergency", which refer to a heterogeneous group of people with hypertensive disorders. Hypertensive urgency (HU) is a rapid and significant increase in blood pressure (BP) (stage III hypertension, systolic blood pressure, SBP>180mmHg and/or diastolic blood pressure, DBP>110 mmHg) presenting in patients with very mild symptoms or asymptomatic patients that do not include hypertension-mediated organ damage (HMOD). These incidents are often associated with poor compliance with antihypertensive therapy, acute stress/anxiety situations, panic attacks, severe pain of various causes, venous epistaxis, or alcohol withdrawal. On the other hand, hypertensive emergencies (HE) describe the above BP rise, associated with new or emerging organ damage, potentially life-threatening. HE requires hospitalization and rapid control of BP, usually using intravenous antihypertensive drugs within minutes or hours [1]. This review focuses on the second group.

Epidemiology

There has been a gradual decline in the mortality rate of patients with hypertensive crises over the last four decades due to the use of new antihypertensive drugs. However, 1–2% of hypertensive patients worldwide are estimated to experience at least one episode of HU or HE in their lifetime. They amount to 0.5–1% of the total number of patients referring

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to the emergency department (ED) and 1% of the total number of patients admitting to the Intensive Care Unit (ICU) in the European continent. Almost a quarter of them concerns HE, and the rest three-fourths include patients with HU [2–4]. The prevalence seems to be higher in the United States of America(2–4%) [5] and developing countries (4–6%) [6]. Heart failure, myocardial infarction, and stroke represent the largest proportion of hypertensive emergencies, followed by intracranial hemorrhage and aortic dissection. In contrast, the incidence of malignant hypertension (i.e., severe hypertension BP>200/120 mmHg, small artery fibrinoid necrosis in the kidney, retina, and the brain) is quite low and probably underdiagnosed [2–6].

Pathophysiology

The mainstay pathophysiological mechanisms involve long-term uncontrolled hypertension accompanied by extremely elevated blood pressure resulting in an acute increase in humoral vasoconstrictors (angiotensin II, norepinephrine) and systemic peripheral resistance as well as augmentation in mechanical stress on the vascular wall. In the sequel, endothelial damage is promoted with an increase in vascular permeability, activation of platelets and coagulation cascade, fibrin deposition, and induction of inflammatory cytokines and oxidative stress. As a result of vascular damage, vasoconstriction and thrombosis lead to hypoperfusion, autoregulatory dysfunction, and end-organ ischemia [7, 8].

Clinical presentation

The clinical picture varies considerably and is dominated by the symptoms of the target organ damage. HE may occur as acute ischemic or hemorrhagic stroke, acute heart failure, acute myocardial infarction, but also as a sympathomimetic crisis (e.g., due to cocaine toxicity, pheochromocytoma), acute aortic dissection, malignant hypertension (microangiopathy, grade III/IV retinopathy, acute renal failure or hypertensive encephalopathy) and eclampsia/preeclampsia/HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets). The symptomatology includes visual disturbances (Keith-Wagener-Barker type III/IV hypertensive retinopathy, malignant hypertension), angina (acute coronary syndrome), thoracic pain (acute aortic dissection), dyspnea (heart failure/pulmonary edema) and focal neurological deficit (stroke), general neurological disorders (cerebral edema-hypertensive encephalopathy) and tonic-clonic seizures (eclampsia) or loss of consciousness. Special reference to the Posterior Reversible Encephalopathy Syndrome (PRES) is needed since it is the main pathogenic mechanism of cerebral angiogenic edema and is characterized by headache, confusion, seizures and vision loss. It is caused mainly by malignant hypertension, eclampsia, autoimmune diseases, and the administration of immunosuppressive therapy. Also, non-specific symptoms may occur in HE, such as dizziness, headache, abdominal pain, nausea, vomiting, anorexia, while few patients remain asymptomatic (e.g., acute renal failure).

The few non-randomized studies so far have identified intense stress, non-compliance with antihypertensive treatment, increased salt intake, abuse of alcohol and substances (cocaine, amphetamines), use of drugs (corticosteroids and mineralocorticoids, estrogens, non-steroidal anti-inflammatory drugs, cyclosporine, carbamazepine, metoclopramide and angiogenic inhibitors/chemotherapy), pheochromocytoma crisis and acute pain as the main causes of HE [2–5]. Hyperadrenergic conditions can be promoted by drug use (e.g., interactions between monoamine oxidase inhibitors and other drugs or foods, cocaine toxicity, amphetamine overdose), withdrawal of short-acting antihypertensive agents (clonidine, β-blockers), and pheochromocytoma. Of course, the history of hypertension is a major risk factor. Other risk factors include obesity, a large number of antihypertensive drugs [9], coronary heart disease, male sex [5], and non-adherence to medication [10].

Diagnosis

All patients with an acute increase in BP require a complete history, with particular attention to pre-existing hypertension and target organ damage, and a detailed clinical examination, aiming at cardiovascular and neurological disorders. BP should be measured according to the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines (3 measurements on both arms in a sitting and standing position, if conditions allow it) [1]. A significant difference in BP between the two arms should increase suspicion of aortic dissection. Repeated measurements of BP should be obtained, as in approximately 30% of patients with HU, an automatic reduction of BP is observed after 20–30 minutes of rest.

Alcohol consumption, ingestion of food (e.g., licorice), use of illicit substances or drugs mentioned above should be thoroughly investigated. Tests should include a 12-lead electrocardiogram, serum electrolytes, creatinine, complete blood count, lactic dehydrogenase, haptoglobin, cardiac enzymes (i.e., troponin, creatine phosphokinase, creatine

kinase-muscle/brain, B-type natriuretic peptide, NT-pro B-type natriuretic peptide), D-dimmers, and in case of possible pregnancy β-human chorionic gonadotropin. In high suspicion of HMOD, fundoscopy should always be conducted regardless of symptoms. Specific examinations such as an echocardiogram, chest radiography, brain computed tomography or magnetic resonance imaging, chest/abdominal contrast-enhanced computed tomography or transesophageal echocardiography for scanning the aorta, kidney ultrasound, and dynamic vascular ultrasound of the renal arteries should be performed according to the clinical picture to complete the puzzle as presented in Figure 1 [8].

Management

The main goal of treatment is to inhibit the worsening of organ damage and avoid long-term complications [8]. Admission to the intensive care unit (ICU) is recommended for continuous hemodynamic monitoring of arterial BP. Immediate intravenous administration of short-acting drugs and their titration, depending on the organic target lesion, is the preferred approach. The reduction of BP should start in a few minutes and increase gradually. The drop in BP required is rapid in all patients except for malignant hypertension, hypertensive encephalopathy, and acute ischemic stroke that should be achieved gradually over several hours and days [1, 8, 11]. The effect of the rapid action of intravenous agents available for the treatment of HE should be carefully monitored to avoid an excessive rate of BP reduction, leading to complications such as acute myocardial infarction and stroke due to hypoperfusion (Table 1). After an appropriate period (often 24 to 72 hours) of BP control, the initial intravenous therapy is shifted to orally administered treatment in neurologically stable patients.

Prognosis and follow-up

Patients presenting to the ED with severe hypertension deserve prompt triage to establish the presence of hypertensive emergency or urgency and further adjusted management. In hypertensive emergencies, the use of parenteral antihypertensive drugs to prevent progression of HMOD and admission in the ICU with continuous blood pressure monitoring is of utmost importance.

Both HE and HU are severe forms of hypertension with recurring visits to the ED. In the few epidemiological follow-up studies, HE are recorded to have the worst prognosis in terms of neurological, cardiovascular events as well as hospitalizations and mortality when compared with HU [8, 13].

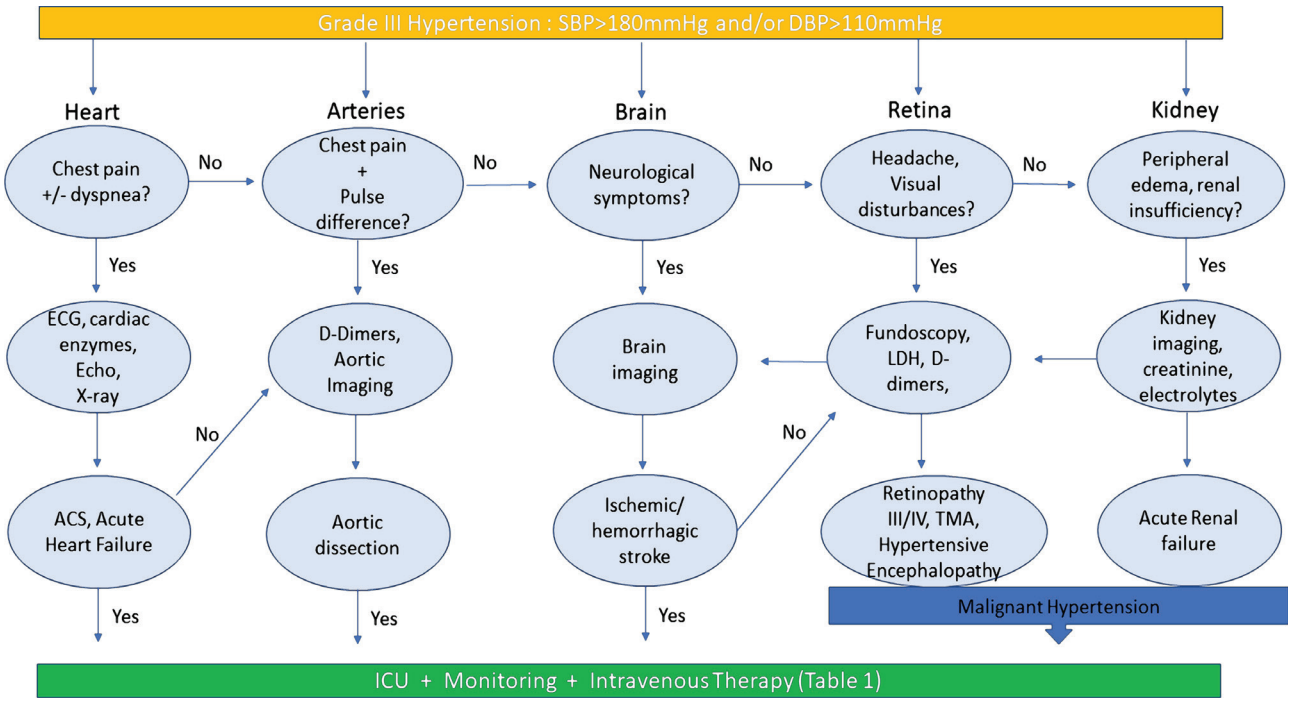

Figure 1. Diagnostic symptom-based algorithm of patients with HE. ACS – Acute coronary syndrome, ECG – electrocardiogram, ECHO – Cardiac and lung ultrasound, LDH – lactic dehydrogenase, TMA – thrombotic microangiopathy, X-ray – Chest Radiography.

Table 1. Hypertensive emergencies and BP lowering target.

Hypertensive emergency	Target of BP decrease and time to achieve	1st line therapy	2nd line therapy	Contraindications
Malignant hypertension (Hypertensive retinopathy, acute renal failure, TMA)	Several hours MAP (20–25%)	Labetalol, Nicardipine	Nitroprusside or Urapidil, hemodialysis or peritoneal dialysis	
Hypertensive encephalopathy	Immediate MAP (20–25%)	Labetalol, nicardipine	Nitroprusside	
Acute ischaemic stroke and SBP>220 mmHg or DBP>120 mmHg				
Acute ischaemic stroke with an indication for thrombolytic therapy and SBP>185 mmHg or DBP>110 mmHg	1h, MAP-15% (or lower when required by comorbidities) 1h, MAP-15%	Labetalol, Nicardipine Labetalol, Nicardipine	Nitroprusside Nitroprusside	
Acute hemorrhagic stroke and SBP>180 mmHg	Immediate, 130<SBP<180 mmHg	Labetalol, Nicardipine	Urapidil	Nitroprusside and Hydralazine
Acute aortic dissection	Immediate, SBP<120 mmHg and heart rate <60 bpm	Esmolol and Nitroprusside or Nitroglycerine or Nicardipine	Labetalol or Metoprolol	β-blockers if severe aortic valve insufficiency or cardiac tamponade (hemopericardium) are suspected
Acute coronary syndrome	Immediate, SBP<140 mmHg	Nitroglycerine, Labetalol	Urapidil	BP>180/10 mmHg is a relative contraindication to thrombolysis
Acute pulmonary edema/heart failure	Immediate, SBP<140 mmHg	Nitroprusside or Nitroglycerine (with a loop diuretic), NIPPV	Urapidil (with loop diuretic)	
Sympathomimetic hypertensive crisis	1h, SBP<140mmHg	Phentolamine, Diazepam and Nitroglycerin	Nitroprusside	Avoid using a beta-blocker before administering phentolamine
Eclampsia/ Preeclampsia/ HELLP syndrome	Immediate, SBP<160 mmHg and DBP<105 mmHg	Labetalol or Nicardipine and Magnesium sulphate	Labor	Nitroprusside

BP – blood pressure; bpm – beats per minute; DBP – diastolic blood pressure; h – hour; HELLP – Hemolysis; Elevated Liver enzymes and Low Platelets; MAP – mean arterial pressure; NIPPV – non-invasive positive pressure ventilation; SBP – systolic blood pressure; TMA – thrombotic microangiopathy. Modified from van den Born *et al.* [8, 12].

Perspectives

For the time being, the management of HU and HE is based on observational studies, experts' opinions, and consensus papers. Future studies should strengthen and complement therapeutic protocols of HE in the form of randomized controlled trials, as well as enlighten short and long-term outcomes of HE and their specific therapies. It is clear that

there should be more intensive follow-up for patients with HE and encourage better medication adherence and recommended lifestyle changes for both groups to improve this clinical entity and its prognosis.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

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