

Treatment of hypertensive emergencies and urgencies

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Abstract

Severe hypertension is a common clinical problem, encountered in various clinical settings. Although various terms have been applied to severe hypertension, such as hypertensive crises, emergencies, or urgencies, they are all characterized by acute elevations in BP that may be associated with end-organ damage (hypertensive emergency). The immediate reduction of BP is only required in patients with acute end-organ damage. Various treatment options, both old and new, exist to manage these patients in the emergency department. Decisions on therapy are patient specific and depend on the underlying cause of elevated blood pressure. Today, a wide range of pharmacologic alternatives are available to the practitioner to control severe hypertension. This article reviews some of the current concepts and common misconceptions in the management of patients with acutely elevated BP. (Revista de Medicină de Urgență, Vol. 4, Nr. 1: 33-43)

Key Words: hypertensive emergency; hypertensive urgency; antihypertensive drugs; emergency treatment.

Introduction

Hypertension is one of the most common worldwide diseases afflicting humans. The manifestations and complications associated with elevated blood pressure (BP) are unpredictable. Terms such as crisis, urgency or emergency, used to describe the acute complications of hypertension, denote an uncontrolled, severe, or abrupt onset of elevated BP, sometimes resulting in a major cardiac, renal, or neurological complication.

A *hypertensive emergency* is a condition in which severe elevation of blood pressure results in acute target organ damage (TOD) (Table 1). In these clinical situations, BP should be reduced immediately, but not necessarily to normal range. A patient with true hypertensive crisis should be treated in an ICU and a parenteral treatment is given preference.

Hypertensive urgency refers to severe hypertension (usually $>180/120$ mmHg) without evidence of new or worsening end-organ injury. Blood pressure can be lowered less rapidly in this condition by orally administered drugs, without hospital admission and with ambulatory follow-up [1].

Thus, the difference between these two forms is the evidence of target organ involvement, not the value of blood pressure.

Initial Assessment

- Hypertensive encephalopathy
- Severe hypertension associated to acute target organ damage:
 - Acute coronary syndromes
 - Pulmonary oedema
 - Acute aortic dissection
 - Intracerebral haemorrhage, subarachnoid haemorrhage
 - Acute brain infarction
 - Acute or rapidly progressing renal failure
- Severe hypertension after thrombolysis for ischaemic stroke
- Pheochromocytoma crisis
- Guillain Barré syndrome
- Spinal cord injury
- Drug-related hypertension (sympathomimetics, cocaine, phencyclidine, phenylpropanolamine, lysergic acid diethylamide, cyclosporin, antihypertensive treatment withdrawal, interaction with monoamine oxidase inhibitors)
- Eclampsia
- Postoperative bleeding
- Post coronary artery bypass hypertension

The history and physical examination determine the nature, severity, and management of the hypertensive event. A brief but thorough history should address the duration as well as the severity of hypertension, pre-existing TOD, all current medications including prescription and non-prescription drugs and, of particular importance, the use of recreational drugs.

The variation of blood pressure is more important than the absolute level of it. The rapidity with which blood pressure increased could compromise the function of target organ in normotensive patient (e.g. preeclampsia, acute glomerulonephritis). The patients with a long history of uncontrolled hypertension can tolerate severe rise of BP without significant acute organ damage [3].

Accurate measurement of blood pressure must be performed, according to current Guidelines [4]: BP should be measured in both sitting and standing position; BP should also be measured in both arms (a significant difference suggests an aortic dissection). In the emergency department, blood pressure should then be strictly monitored.

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The physical examination should include a careful search for damage to target organs and for features of various identifiable causes [5]:

- general appearance – distribution of body fat, skin lesions, muscle strength, alertness;
- waist circumference – the values exceeding 88 cm in women and 102 cm in men are indicative of abdominal obesity and the metabolic syndrome and serve as a cardiovascular risk factor independent of weight;
- funduscopy – the presence of new retinal hemorrhages,

exudates, or papilloedema suggests a hypertensive emergency;

- neck – palpation and auscultation of carotids, thyroid;
- heart – size, rhythm, sounds;
- lungs – rhonchi, rales;
- abdomen – renal masses, bruits over aorta or renal arteries, femoral pulses;
- extremities – peripheral pulses, edema;
- neurological assessment – level of consciousness, visual fields, focal neurological sign.

The clinical characteristics of a hypertensive emergency are listed in table 2.

Table 2 . Clinical Characteristics of the Hypertensive Emergency [6]

Blood Pressure	Funduscopy findings	Neurological status	Cardiac findings	Renal symptoms	Gastrointestinal symptoms
Usually >220/140 mmHg	Hemorrhages, exudates, papilloedema	Headache, confusion, somnolence, stupor, visual loss, seizures, focal neurological deficits, coma	Prominent apical pulsation, cardiac enlargement, congestive heart failure	Azotemia, proteinuria, oliguria	Nausea, vomiting

Patient's History should focus on the duration of the elevated BP and any prior treatment, the current use of various drugs that may cause it to rise, and symptoms of target organ dysfunction (table 3). An area of great importance is sexual dysfunction, often neglected until it arises after antihypertensive therapy is given. Erectile dysfunction, often attributed to antihypertensive drugs, may be present in as many as one-third of untreated hypertensive men and is most likely related to their underlying vascular disease [5].

Laboratory Testing

For most patients, a blood chemistry (creatinine, urea, glucose, electrolytes), a lipid profile (LDL, HDL, cholesterol, triglycerides), a full blood count, urinalysis, a 12-lead electrocardiography and a chest X rays are all the routine procedures needed. The serum creatinine should be adjusted with the patient's age, gender, and weight to calculate the GFR using the MDRD (Modification of Diet in Renal Disease) formula.

Additional Testing

When a secondary form of hypertension is suspected, a sample for plasma renin activity, aldosterone and eventually catecholamine should also be drawn. Further investigation (according to the clinical presentation) [2]:

- echocardiography (TT, TE);
- brain CT or MRI;
- abdominal ultrasonography;
- thoraco-abdominal CT scan or MRI;
- vascular ultrasound.

Treatment of hypertensive emergencies

Patients should be admitted to an ICU for clinical surveillance and continuous blood pressure monitoring. Parenteral drugs will be preferred, but the initial goal should be a partial reduction (and not normalization) of blood pressure, with a reduction of no more than 20-25% within the first minutes up to one or two hours, with possible cautious further decreases in subsequent hours [7]. In most hypertensive emergencies, a rapid lowering of BP values is beneficial, with the exception of cerebrovascular accidents (where a more cautious approach necessary) [8]. An excessive reduction of BP is potentially dangerous, possibly leading to ischaemic complications such as myocardial infarction, stroke or blindness in some cases [9].

A number of parenteral antihypertensive drugs are available for the treatment of hypertensive emergencies (table 4).

The choice of first-line antihypertensive agent should be tailored to the patient's clinical status.

Table 3. Important Aspects of the Patient's History

Duration of the hypertension Last known normal blood pressure Course of the blood pressure Prior treatment of the hypertension Drugs: types, doses, side effects Intake of agents that may interfere Nonsteroidal anti-inflammatory drugs Oral contraceptives Sympathomimetics Adrenal steroids Excessive sodium intake Alcohol (>2 drinks/day) Herbal remedies Family history Hypertension Premature cardiovascular disease or death Familial diseases: pheochromocytoma, renal disease, diabetes, gout Symptoms of secondary causes Muscle weakness Spells of tachycardia, sweating, tremor Thinning of the skin Flank pain Symptoms of target organ damage Headaches Transient weakness or blindness Loss of visual acuity Chest pain Dyspnoea Edema Intermittent Claudication	Presence of other risk factors Smoking Diabetes Dyslipidemia Physical inactivity Concomitant diseases Dietary history Weight change Fresh vs. processed foods Sodium Saturated fats Sexual function Features of sleep apnea Early morning headaches Daytime somnolence Loud snoring Erratic sleep Ability to modify lifestyle and maintain therapy Understanding the nature of hypertension and the need to follow a regimen Ability to perform physical activity Source of food preparation Financial constraints Ability to read instructions Need for care providers
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Sodium nitroprusside is the drug of choice in most hypertensive emergencies because it has a rapid onset and a short duration of action with almost universal effectiveness. In patients with primary intracerebral haemorrhage, caution is needed because of a potential antiplatelet effect and intracranial pressure increase. Constant monitoring of the BP is required for titration of its effects. Hypotension can be managed in most cases by discontinuing the infusion. Nitroprusside decreases both systemic arterial and venous tone equally and reduces myocardial oxygen consumption and cardiac preload and afterload. Cardiac output is generally unaffected, but may improve in patients with heart failure. Nitroprusside is not a drug of choice in eclampsia because it crosses the placenta.

Nitroprusside is non-enzymatically converted to cyanide, which is then converted enzymatically to thiocyanate and excreted in the urine. Thiocyanate toxicity, which usually manifests as confusion, hyperreflexia, blurred vision, and tinnitus, is unusual at a rate < 2 mg/kg/min for up to 72 hours. Rarely, thiocyanate toxicity may be fatal [10]. Blood thiocyanate levels should be monitored during high-dose or prolonged administration of nitroprusside or if the drug is used

in patients with renal or hepatic impairment. The levels should be maintained below 10 mg/dl to avoid thiocyanate toxicity [11]. An infusion of sodium thiosulphate can be used in affected patients to provide a sulphur donor to detoxify cyanide into thiocyanate [10].

Intravenous nitroglycerin is a venous and, to a lesser degree, arteriolar dilator, lowers myocardial oxygen consumption, and improves coronary artery perfusion. Nitroglycerin is the drug of choice in hypertensive emergencies complicated by pulmonary edema or acute coronary syndromes and hypertension following coronary by-pass because it can improve coronary perfusion better than nitroprusside. On the other hand, its effectiveness is less predictable than nitroprusside; hence, it should not be considered as first-line therapy in other situations. Hypotension and reflex tachycardia (resulting from reflex sympathetic activation) may develop in the presence of volume depletion. Headache can be due to direct vasodilatation. Prolonged use may result in tolerance. Cyanide accumulation does not occur.

Enalaprilat is an intravenous preparation of the active form of the angiotensin converting enzyme inhibitor enalapril. It is administered in an iv dose of 1.25 mg and may

be repeated at 6-hour intervals. Response to enalaprilat in hypertensive emergencies is unpredictable, in part because of variable degrees of plasma volume expansion. Like other ACE inhibitors, the Enalaprilat hypotension effect is associated with the plasma renin level. The patients with low renin plasma can have a minimal tensional response. Enalaprilat given iv is the most efficient for patients with severe hypertension and high renin plasma level (such as renal vasculitis). This agent may be particularly suitable in hypertensive emergencies associated with congestive heart failure. Enalaprilat, like other ACE inhibitors, are contraindicated in pregnancy.

Labetalol is an alpha and beta-adrenergic blocker, which can be given as an 20 mg intravenous bolus, followed by 20-80 mg every 10 min to a total dose of 300 mg. Labetalol reduces PVR with a minimal (or without) change of cardiac output, ventricular rate or cerebral blood flow. It is highly effective and is useful in most hypertensive emergencies, especially in aortic dissection and in acute coronary syndromes. It may be given also after cocaine or amphetamine use that may induce transient but significant hypertension leading to stroke and/or serious cardiac damage. Labetalol should generally be avoided in patients with asthma, chronic obstructive lung disease, congestive heart failure, bradycardia or greater than first-degree heart block. Labetalol's side-effects are as follows: flush, orthostatic hypotension, vomit, scalp paraesthesia.

Diuretics must be given to patients with pulmonary edema and cardiac failure. Most of the patients with emergency hypertension have a certain level of intravascular volemic loss, possibly of natriuresis induced by the associated pressure. If diuretics are administered in this situation they could exacerbate the hypertension (via reflex vasoconstriction) and the renal function could be compromised. Furosemide (40-60 mg) or Bumetanide (1-5 mg) could be repeatedly administered intravenously for an adequate renal output.

Fenoldopam is a selective, peripheral dopamine-1 receptor agonist that induces systemic vasodilatation, particularly in the renal circulation [12]. This agent also has effects on renal proximal and distal tubules. This drug does not cross the blood/brain barrier. Fenoldopam does not bind to dopamine-2 receptors or beta-adrenergic receptors; it has no alpha-adrenergic agonist effects but is an alpha-1 antagonist. Fenoldopam's unique effects on the kidney provide increased urine flow rate, sodium and potassium excretion, and improved creatinine clearance, making this agent particularly attractive in hypertensive emergencies associated with significant renal impairment. Fenoldopam could maintain the urinary output and renal function even if there is low blood pressure; it has direct natriuretic properties at the renal tubules level [13]. It maintains most of its efficacy for 48 hours of constant rate infusion without rebound hypertension when discontinued. Fenoldopam provides clinical effects similar to those of nitroprusside in improving car-

diac hemodynamics in patients with acute congestive heart failure [14]. Onset of clinical effect is seen within 5 minutes, and effects tend to dissipate within 30 minutes of discontinuing the infusion. The most common side effects include headache, flushing, tachycardia, and dizziness. A dose-related increase in intraocular pressure has been observed in normotensive and hypertensive patients, thus fenoldopam is contraindicated in patients with glaucoma [15]. Inactive metabolites are eliminated in the urine, and no dosage adjustments are required for patients with renal or hepatic impairment.

Nicardipine is an i.v. form of the dihydropyridine calcium antagonist and is effective in a high percentage of hypertensive emergencies, particularly at higher infusion rates. Its growing popularity can be attributed to its ease of administration. Infusion rates can be increased by 2.5 mg/hr at intervals of 15 to 20 minutes until the maximal recommended dosage of 15 mg/hr is obtained or until the desired reduction in BP is achieved. Dosing of nicardipine is not dependent on body weight. Nicardipine has been shown to reduce both cerebral and coronary ischemia. Because it does not increase the intracranial pressure, Nicardipine is given especially in emergency hypertension cases associated with neurological complications. Intravenous nicardipine (2.5 to 15mg/h) appears to be as effective as nitroprusside in the treatment of postoperative hypertension and has fewer side effects. Nicardipine produces coronary dilatation but increases the ventricular rate. It also increases the workload of the heart and the oxygen requirements at the same time. In this case it is not recommended in emergency hypertension associated with acute coronary syndrome. Headache, nausea, and vomiting may occasionally be observed. The major limitation is a longer half-time, which precludes rapid titration.

Hydralazine is a direct arteriolar vasodilator used primarily in eclampsia; it maintains the fetal perfusion much better than the other antihypertensive drugs and the uterine blood flow is ameliorated. One of its side-effects is an increase of the intracranial pressure, so in this case hydralazine is contraindicated in complicated hypertensive crises with ischemic stroke, intracerebral or subarachnoid hemorrhage. It may cause a rapid fall in BP and significant reflex tachycardia. Hydralazine is contraindicated in ischemic heart disease and aortic dissection [16]. The hypotensive response to hydralazine is less predictable than that seen with other parenteral agents and its current use is primarily limited to pregnant women.

Phentolamine is a nonselective alpha-adrenergic blocking agent that is still used when excess catecholamine states, such as pheochromocytoma or tyramine ingestion in a patient being treated with a MAO inhibitor, are suspected. It is useful as a diagnostic agent when administered as a bolus injection of 5 to 10 mg in patients with suspected pheochromocytoma. Acute BP lowering will be seen within several minutes and may last 10 to 30 minutes. Tachycardia is common and on occasion may precipitate myocardial

Table 4. Parenteral drugs for treatment of hypertensive emergencies [2]

Drug	Dose	Onset	Duration	Side effects
Sodium nitroprusside	0.25-10 g/kg/min*	immediate	1-2 min	Hypotension, vomiting, sweating, cyanide toxicity
Glyceryl trinitrate	5-100 g/min	1-3 min	5-15 min	Headache, vomiting, tolerance with prolonged use
Enalaprilat	1.25-5 mg bolus	15 min	4-6 h	Hypotension, renal failure, angioedema
Labetalol	20-80 mg bolus, 1-2 mg/min piv	5-10 min	2-6 h	nausea, vomiting, scalp tingling, heart block, bronchospasm, orthostatic hypotension
Furosemide	40-60 mg	5 min	2 h	Hypotension
Fenoldopam	0.1-0.6 g/kg/min	5-10 min	10-15 min	hypotension, headache, nausea
Nicardipine	2-10 mg/h	5-10 min	2-4 h	Reflex tachycardia, flushing, local phlebitis
Hydralazine	10-20 mg bolus	10 min	2-6 h	Reflex tachycardia, headache, vomiting, aggravation of angina
Phentolamine	5-10 mg/min	1-2 min	3-5 min	Reflex tachycardia, flushing
Urapidil	25-50 mg bolus	3-4 min	8-12 h	Sedation

REVISTA DE MEDICINĂ DE URGENȚĂ

ischemia. Nitroprusside and labetalol are more easily titrated in the management of hypertensive emergencies associated with high circulating levels of catecholamine, and therefore phentolamine is rarely used therapeutically today.

Urapidil is an alpha-blocker with additional actions in the central nervous system (it activates 5-HT_{1A} receptors). It has also been found effective in some hypertensive emergencies, since it induces vasodilatation without tachycardia [2].

Esmolol is an ultra-short-acting beta-adrenergic blocker (half-life is about 9 min and total duration of action is 30 min) that is administered intravenously. Onset of effect is seen almost immediately, with a rapid offset of effect within 15 to 30 minutes after discontinuation. Esmolol may be administered as a 500-μg/kg bolus injection, which may be repeated after 5 minutes. Alternatively, an infusion of 50 to 100 μg/kg/min may be initiated and increased to 300 μg/kg/min as needed. Esmolol has found particular use during anesthesia to prevent postintubation hemodynamic perturbations. Adverse effects include increased heart block, precipitation of congestive heart failure, and bronchial spasm.

Non-dihydropyridine calcium channel blockers, particularly Verapamil, appear to be safe in the treatment of

post infarction hypertension [17]. Verapamil can also be used in aortic dissection when beta-blockers are contraindicated.

Specific hypertensive emergencies

Acute coronary syndromes frequently increase the blood pressure. Myocardial ischemia may also be induced by acute elevations in BP in patients without haemodynamically relevant coronary artery disease through an increase in LV wall stress and myocardial oxygen consumption.

There may be an opposite relationship between hypertension and acute coronary syndrome. Therefore the hyperalgalic onset of acute myocardial infarction (AMI) could induce an urgency hypertension at the onset of myocardial necrosis. The high BP values return to normal within 6 hours of the AMI onset. Even if the chest pain is well controlled, if the BP values are maintained over 160/100 mmHg for more than 1 hour, then it is necessary to initiate an antihypertensive treatment. It is very important to maintain the blood pressure within the normal limits as much as possible; this is useful for reperfusion therapy. Thrombolysis is not recommended if the BP is higher than 200/120 mmHg.

Lowering the output should be carefully done because myocardial perfusion is dependent on the pressure of coronary perfusion. The episodes of low blood pressure might aggravate myocardial ischaemia and the width of the infarct.

The drugs that reduce the output and improve the coronary flow are useful. One of them is *Nitroglycerin*; it is the elected drug if it is administrated iv because it produces dilation of the intercoronary arteries more than the resistant vessels. Additionally, Nitroglycerin also decreases the input. *Nitroprusside* has its main effect on the resistant vessels and might have “coronary stalling” effect. It is given only when nitrates treatment does not work.

Beta-blockers (labetalol, metoprolol, esmolol or atenolol) are also effective and may further decrease BP and reduce heart rate, and, consequently, myocardial oxygen consumption.

Drugs that increase cardiac work and myocardial oxygen consumption (hydralazine, diazoxide, short acting dihydropyridine) are contraindicated.

Acute left ventricular failure and acute pulmonary edema

Acute left ventricular failure (LVF), as well as a severe form of acute pulmonary edema (APE) may appear in hypertension because of impairment of diastolic function, even if the systolic function is preserved, or it might appear if the systolic ventricular function is altered. Therefore the acute LVF caused by the hypertension could be present on a normal volume heart with an important LV hypertrophy or on a dilated heart. Acute LVF could be triggered by arrhythmias, myocarditis etc.

The persistence of high BP values and associated signs and symptoms of affected organ damaged targets are specific for hypertensive APE, even if the signs of acute left ventricular failure are reduced. Also, other etiological types of cardiogen APE could lead to an important increase in blood pressure, because of a sympathetic reaction. If the pulmonary congestion is reduced, the values of blood pressure also decrease, even if there is no antihypertensive treatment.

Treatment should be started immediately with vasodilators drugs (especially venous dilators – *Nitroglycerine*) or with mixed action (*Nitroprusside*), associated with loop diuretics (*Furosemide*). In less emergency situations, *ACE inhibitors* could be used.

Drugs that increase cardiac work (hydralazine) or decrease cardiac contractility (labetalol or other beta-blockers) should be avoided.

Aortic dissection

In patients with aortic dissection and hypertension, BP control is crucial. The stresses that damage the vessel wall are related to the mean pressure, the width of the pulse pressure, and the maximal rate of rise of the pressure (dp/dt). Drugs that diminish dp/dt are the optimal agents to treat a dissection [18]. The antihypertensive treatment should be

started immediately. The initial aim of medical therapy in such patients is to decrease both the systemic BP (to a systolic pressure of 100 to 120 mmHg or less if tolerated) and heart rate and cardiac contractility. These combined goals are usually achieved by the combination of a vasodilator – *nitroprusside* or *nitroglycerine* – and an intravenous beta-blocker such as propranolol or labetalol. Nitroprusside should not be given without a beta-blocker.

Acute increase in sympathetic activity

In addition to drug withdrawal, increased adrenergic activity can lead to severe hypertension in a variety of other clinical settings. These include: pheochromocytoma; autonomic dysfunction (as in the Guillain-Barré syndrome or post-spinal cord injury); the use of sympathomimetic drugs, such as phenylpropanolamine, cocaine, amphetamines, phencyclidine, or the combination of an MAO inhibitor and the ingestion of tyramine-containing foods (such as most fermented cheeses, smoked or aged meats, Chianti, champagne, and avocados) [1,19]. The rise in BP seen in the last setting is due to an MAO inhibitor-induced decline in intestinal tyramine metabolism, followed by increased tyramine absorption and a subsequent tyramine-induced release of endogenous catecholamine.

Control of the hypertension in these disorders can be achieved with phentolamine, labetalol, or nitroprusside. *Phentolamine*, an intravenous alpha-blocker, is the drug of choice in management of pheochromocytoma crisis or excess catecholamine states. It should be followed by the concomitant infusion of a beta-blocker. *Nitroprusside* may also be added. *Labetalol* as monotherapy is a good choice; it achieves a simultaneous alpha- and beta-blockade.

Administration of a beta-blocker alone is contraindicated, since inhibition of beta-receptor-induced vasodilatation results in unopposed alpha-adrenergic vasoconstriction and a further rise in BP [20].

Acute ischemic stroke or subarachnoid or intracerebral hemorrhage

The benefit of reducing the BP in these disorders must be weighed against possible worsening of cerebral ischemia induced by the thrombotic lesion or by cerebral vasospasm. Autoregulation of blood flow is impaired in ischemic areas of the brain and BP reduction may further expand the size of the infarction.

These cerebrovascular events are characterized by the abrupt onset of usually focal neurological findings. This is in contrast to the typically insidious onset of headache, nausea, vomiting, and confusion seen in hypertensive encephalopathy, a disorder in which rapid lowering of the BP generally leads to resolution of the symptoms within 24 to 48 hours.

In patient with **acute ischemic stroke**, the use of antihypertensive therapy is still controversial. It seems reasonable to recommend the initiation of antihypertensive

treatment only in the presence of BP values $> 220/120$ mmHg (or mean BP > 140 mmHg) and to obtain an initial reduction of BP values of about 10-15%. Treatment may be initiated with intravenous *labetalol*, and, if needed, with *nitroprusside* or *nitroglycerin* [2]. In patients with acute stroke treated with thrombolysis, BP should be kept below 185/110 mmHg.

In **intracerebral hemorrhage**, treatment should be started if BP values are greater than 180/105 mmHg [2].

Eclampsia

Intravenous *hydralazine* is the treatment of choice in pregnant women with severe hypertension (usually due to preeclampsia or preexistent hypertension). *Nicardipine* or *labetalol* are alternatives in patients who do not achieve adequate BP control with *hydralazine*.

In contrast, *nitroprusside* (which may cause cyanide intoxication in the fetus), angiotensin converting enzyme inhibitors (which can impair renal function in the fetus), and angiotensin II receptor blockers are contraindicated in pregnancy.

Acute postoperative hypertension is frequent after cardiothoracic, vascular, head and neck, and neurosurgical procedures. For most non-cardiac types of surgery there is no agreement on BP thresholds for treatment, and it seems reasonable to maintain BP within 20% of preoperative arterial pressure [21]. For cardiothoracic surgery, there is more evidence of an increased risk associated with a postoperative increase in BP values, which should be kept below 140/90 mmHg [21, 22]. *Labetalol* (and other beta-blockers), *nitroprusside*, *nitroglycerin*, or *fenoldopam* should be preferred to intravenous drugs for BP control [2]. A good analgesia and an adequate volemic status might be beneficial.

Hypertensive encephalopathy is a clinical syndrome represented by neurological symptoms (sometimes very severe) such as: headache, central sickness, vomiting, confusion, drowsiness, agitation, vision troubles and even vision loss, weakness, generalized convulsions, or sometimes consciousness status alteration until coma. On funduscopy examination we can see grade IV of retinopathy with papillary oedema [3]. Usually, hypertensive encephalopathy appears on patients with chronic hypertension because of severe increase of blood pressure values (DBP > 120 -130 mmHg and variable SBP) which are very difficult to control by drugs or with patients previously normotensive but with a sudden increase in blood pressure values.

Physiopathology of the hypertensive encephalopathy is represented by the diffused cerebral oedema caused by cerebral autoregulation loss. The capillary endothelium is damaged and it leads to an increase of its permeability.

Hypertensive encephalopathy is a great hypertensive emergency and a parenteral antihypertensive treatment must

be administrated in a carefully manner to avoid a rapid decrease in BP, especially in elderly people. Mean BP has to decrease by 25 % in the first 1-2 hours or the DBP should be decreased at about 100 mmHg [11]. If the mean BP is reduced by more than 40% in the first hours, then neurological complications are more likely. If the patient's mental state deteriorates under the treatment, the BP should be allowed to increase slightly and then initiate a slow reduction in BP. If the neurological symptoms still persist after decreasing the BP values, then another diagnosis should be considered.

The best drugs used in the hypertensive encephalopathy treatment are *Nicardipine*, *Nitroprusside*, *Labetalol* and *Fenoldopam*.

Central inhibitor adrenergic drugs cannot be given because they have a sedative effect (*Clonidine*, *Metil-Dopa*, *Rezerpine*, beta-blockers) and also the direct vasodilators (*Diazoxid*, *Hidralazine*) which may increase the cerebral vasodilation.

Malignant and accelerated hypertension

Accelerated or malignant hypertension is a clinical syndrome in which elevated blood pressure is associated with:

- target organ damage (progressive renal failure, retinopathy, cardiac failure);
- rapid evolution of histological lesions;
- relatively resistant to antihypertensive treatment.

Accelerated hypertension is defined as a significant increase over baseline blood pressure (usually DBP > 130 mmHg) that is associated with hemorrhages and retinal exudates (retinopathy stage III), while malignant hypertension is associated with papillary oedema (retinopathy stage IV). Hypertensive retinopathy is associated with malignant nephroangiosclerosis resulting in fibrinoid necrosis in renal microcirculation and with microangiopathic hemolytic anemia. Fibrinoid necrosis could also appear in myocardial and cerebral circulation.

Actually, it is more appropriate to include malignant and accelerated hypertension as hypertensive emergencies complicated by retinopathy or papillary oedema [3].

Malignant hypertension is characterized by vascular modifications and extremely high BP values. Fibrinoid necrosis and myointimal proliferation produce acute vascular lesions which harm the renal and cerebral microcirculation. Increased endothelial permeability leads to extravasation of plasmatic components and deposition in the vascular wall and then, oedema, thrombosis and ischaemia. Renal ischaemia leads to activation of the renin-angiotensin system that can cause further elevation of blood pressure and progressive vascular damage. Spontaneous natriuresis early in the course of malignant hypertension leads to volume depletion with activation of the renin-angiotensin system or cat

Table 5: Treatment in hypertensive emergencies

Emergency	Special indications	Contraindicated drugs
Acute coronary syndrome (myocardial infarction, unstable angina)	Nitroglycerin Nitroprusside Beta-blockers	Diazoxide Hydralazine Short acting DHP
Acute left ventricular failure or acute pulmonary edema	Nitroprusside Loop diuretics Enalaprilat	Hydralazine Beta-blockers
Aortic dissection	Nitroprusside Nitroglycerin Propranolol Labetalol	Diazoxide Hydralazine
Adrenergic crisis	Phentolamine Beta-blockers Nitroprusside Labetalol	Beta-blocker alone
Ischemic stroke or subarachnoid or intracerebral hemorrhage	Labetalol Nitroprusside Nitroglycerin Nimodipine (in SAH)	Diazoxide Hydralazine
Eclampsia	Hydralazine Labetalol Nicardipine	Nitroprusside Enalaprilat Angiotensin receptor blockers
Acute postoperative hypertension	Labetalol Nitroglycerin Nitroprusside Nicardipine Fenoldopam	Diazoxide Hydralazine Central inhibitor adrenergic drugs
Hypertensive encephalopathy	Nitroprusside Nicardipine Labetalol Fenoldopam	
Malignant hypertension (when iv therapy is indicated)	Labetalol Nicardipine Nitroprusside Fenoldopam Enalaprilat	

DHP = dihydropyridine; SAH = subarachnoid or intracerebral hemorrhage;

echolamine that further elevates blood pressure. Activation of the clotting cascade within the lumen of damaged vessels may lead to fibrin deposition with localized intravascular coagulation.

The complex pathogenic mechanisms involved in malignant and accelerated hypertension require usually a combined antihypertensive therapy, especially vasodilator drugs.

Treatment aim is to decrease the DBP by approximately 100-105 mmHg over the first 2-6 hours. The initial goal of therapy is to reduce the mean arterial pressure by approximately 25%. Gradual lowering of BP permits necrotic vascular lesions to heal and no evidence suggests a benefit from rapidly reducing blood pressure in these patients. In fact, an aggressive therapy may harm the patient, resulting in cardiac, renal, or cerebral hypoperfusion.

The parenteral agents are often used in cases of malignant hypertension: *Nitroprusside*, *Nicardipine*, *Labetalol*, *Fenoldopam*. Oral agents are not indicated as a first line because they have a slow onset of action and variable hypotensive response. If the parenteral agents are not available, 25 mg of *Captopril* could be administered per lingual; the BP will be reduced in about 10-30 min. A combination of oral agents should be instituted after the BP has been controlled with parenteral medication. The reduction of DBP to 85-90 mmHg will be gained in about 2-3 months. Initially there is a transitory decline in renal function, which will improve in 1-3 months at the same time as renal perfusion improvement.

Even if the antihypertensive treatment is efficient, there is a high risk in patients with malignant hypertension to develop coronary, cerebrovascular and renal diseases. The survival rate at 5 years is about 60-70% [3].

Treatment of hypertensive urgencies

The more common form of hypertensive crisis – *hypertensive urgency* – does not result in symptoms or signs indicative of acute target organ damage. Instead, headache and epistaxis are the two most common symptoms. Although this condition requires medical attention, treatment is not needed immediately. Blood pressure should be lowered gradually over a period of 24-48 hours. This can often be achieved by orally administered drugs, without hospital admission and with close ambulatory follow-up. Clinical surveillance is advisable during the first few hours after drugs administration.

The rapidity with which BP should be brought to safe levels (e.g. <160/100 mmHg) is controversial. A relatively rapid reduction in BP was recommended in the past and a variety of oral therapeutic modalities have been used, including clonidine, sublingual nifedipine, and oral or sublingual captopril. In many cases, however, blood pressure may decline spontaneously simply with rest in a quiet room [23]. Furthermore, there is no proven benefit from rapid reduction of the BP in patients with severe asymptomatic hyper-

Table 6: Drugs for hypertensive urgencies [2]

Drug	Dose	Time to peak	Half life	Side effects
Captopril	12,5-25 mg	15-60 min	1,9 h	Renal failure in renal artery stenosis
Labetalol	200-400 mg	20-120 min	2,5-8 h	Bronchospasm, depression of myocardial contractility, AV block, nausea, elevation of liver enzymes
Furosemide	25-50 mg	1-2 h	0,5-1,1 h	Volume depletion
Amlodipine	5-10 mg	1-6 h	30-50 h	Headache, tachycardia, flushing, peripheral edema
Felodipine	5-10 mg	2-5 h	11-16 h	Headache, tachycardia, flushing, peripheral edema
Isradipine	5-10 mg	1-1,5 h	8-16 h	Headache, tachycardia, flushing, peripheral edema
Prazosin	1-2 mg	1-2 h	2-4 h	Syncope (first dose), palpitations, tachycardia, orthostatic hypotension

tension who have no evidence of acute TOD and the precipitous fall in BP could do more harm than good [2]. In fact, cerebral or myocardial ischemia can be induced by aggressive antihypertensive therapy if the blood pressure falls below the range at which tissue perfusion can be maintained by autoregulation. This has been most often described with sublingual nifedipine; the degree of blood pressure reduction cannot be controlled or predicted, and severe ischemic complications have ensued. Given these concerns, sublingual nifedipine should not be used in this setting [24].

Thus, in the absence of signs of acute end-organ damage, the goal of management is to reduce the blood pressure to 160/100 mmHg over several hours to days. No specific drug has been shown to be particularly efficacious in treatment of hypertensive urgencies. In table 6, recommended oral agents are reported. Patients who present with severe hypertension will probably require a combination of drugs. Depending on the patient, a calcium channel blocker (but not sublingual nifedipine), a beta-blocker or an ACE inhibitor can be started. The approach varies depending on whether the patient has already been treated for hypertension or is untreated.

After administration of medication, patients should be monitored in the office or emergency department for 1 to 2 hours to ensure that there has been a response to treat-

ment with no side effects. For example, marked hypotension may be caused by ACE-inhibitor therapy in patients with renal artery stenosis. Follow-up in 24 to 48 hours is recommended, with continued tailoring of therapy as needed.

Conclusion

Hypertensive emergencies and urgencies are associated with significant morbidity and mortality. Prompt recognition and early treatment is crucial in preventing or halting progressive target organ damage. Frequent monitoring that is typically only feasible in the intensive care unit is necessary to achieve appropriate therapeutic endpoints. Treatment must be tailored to each patient, based on the presence of specific target organ damage and underlying comorbidities. The benefits of treating severe hypertension must be weighed against the risk of excessive blood pressure lowering. There are no high-quality prospective studies that address how quickly and to what degree blood pressure should be lowered. Extensive counseling should be provided to patients upon discharge, especially if noncompliance with medications contributed to the hypertensive crisis syndrome.

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