Hypertensive Emergencies – On The Cutting Edge
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Objectives:

1. Describe severe blood pressure elevation in the emergency department, highlighting features which distinguish true hypertensive emergencies from other conditions
2. Describe the basic pathophysiology which contributes to and results from a hypertensive emergency
3. Describe hypertensive emergency management guided by target-organ specific therapeutic intervention and blood pressure reduction goals

Introduction

Hypertension (HTN) is one of the most important chronic medical conditions, affecting close to 75 million Americans\(^1\) and approximately 1 billion people worldwide.\(^2\) The current burden of HTN reflects a steady rise in disease prevalence over the past two decades, which, at least in the United States, has been accompanied by greater levels of awareness, treatment and blood pressure (BP) control. Hypertension is defined by the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure\(^3\) [JNC 7] as a BP > 140/90 mm Hg for most and > 130/80 mm Hg for individuals with diabetes mellitus or chronic kidney disease.\(^4\) Despite the trend towards an increase in BP control, overall rates of HTN remain suboptimal with persistent elevation in nearly 50%.\(^4\) Among those with poorly controlled HTN, almost 1 in 5 (11.5% overall) have exceedingly high BPs, defined as > 160/100 mm Hg, the JNC 7 cut-off for Stage II HTN, a circumstance which is particularly concerning considering that the independent risk of pressure-related cardiovascular mortality is known to double with each 20/10 mm Hg rise in BP above the “ideal” level of 115/75 mm Hg.\(^1\)

These data have important implications for clinicians in the emergency department (ED) where elevated BP and its associated consequences are commonly encountered.\(^5\) According to the National Hospital Ambulatory Medical Care Survey, 2.9% of the 115 million ED visits in 2005 were related to chronic HTN, up from 2.1% in 1995. In 2006, 16.2% of those treated in EDs across the US, approximately 15 million patients, had an initial BP that was “severely high”, for example ≥ 160/100 mm Hg.\(^6,7\) The vast majority of patients with substantially elevated BP in the ED are asymptomatic and, untreated, their BP will often diminish within a few hours of ED arrival.\(^8,9\) Yet ED management is frequently directed towards pharmacological reduction of the numerical BP value.\(^10\) This may be attributable to confusion regarding the risk profile of patients with HTN and a consequent failure to differentiate true hypertensive emergencies which warrant immediate intervention to arrest potentially fatal acute end-organ damage\(^13\) from simple BP elevations that portend long-term risk but carry a low likelihood of near-term adverse events.\(^14,15\)

What Is a Hypertensive Emergency?

While the term “hypertensive crisis” has been used to categorize any patient whose BP exceeds a certain threshold, often systolic BP ≥ 180 or diastolic BP ≥ 110-120 mm Hg,\(^16-18\) there is limited evidence to suggest that BP alone provides sufficient granularity to direct emergent decision making. Moreover, as noted by Shayne and Pitts in their comprehensive review, use of this term is misleading as most with a severely elevated BP in the ED are not at risk for acute, or even subacute, development of pressure-mediated consequences.\(^19\) Alternative terminology (Table 1) focused on the presence or absence of signs or symptoms attributable to acute target-organ damage within the context of severe HTN has been widely promulgated and serves to distinguish those with active vasculopathy from those without.\(^10,19-22\) As so defined, hypertensive emergencies constitute the subset of patients who present with acute end-organ damage and evidence of organ system dysfunction (Table 2). Though still used by some, often inappropriately, the terms “accelerated” and “malignant” HTN are applicable only to those patients with acute BP elevations which are
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Pathophysiology

Although some hypertensive emergency patients will present de novo with elevated blood pressure, most episodes are triggered by an acute rise in systemic vascular resistance superimposed on underlying chronic HTN. In either case, the etiology is usually idiopathic, such as "primary" or "essential" HTN, with an identifiable cause, such as "secondary" HTN, in fewer than 10% (Table 3).

From a macrocirculatory standpoint, hypertensive emergencies resemble uncomplicated instances of uncontrolled chronic HTN but on a microcirculatory level, they differ greatly. This is due in large part to the rate of BP rise, which is more abrupt in those with a hypertensive emergency and neurohormonal activation, accompanied by retinal hemorrhage or papilledema, respectively. Regardless, such ocular findings are still considered target-organ damage and can be aptly described using more generalizable terminology like hypertensive emergency.
specifically, the sympathetic nervous and renin-angiotensin-aldosterone systems, which often precipitates the acute event. The net result is an overwhelming of vascular autoregulation, which serves to maintain a relatively constant blood flow when confronted by changing pressure dynamics, with local mechanical stress and endothelial injury. The latter leads to reduced endothelial nitric-oxide synthase (eNOS) function and a drop in nitric-oxide mediated vascular smooth muscle relaxation. This, coupled with excess release of endothelin, causes a profound increase in systemic vascular resistance through arteriolar constriction. The cycle is thus self-perpetuating with an initial inciting factor setting off a cascade of effects that functionally maintains BP at severely elevated levels. Without interruption of microcirculatory dysfunction, perfusion distal to the arterioles begins to decrease and a proinflammatory, hypercoagulable state with fibrinoid necrosis and regional ischemia develops. At the macrocirculatory level, sustained elevations in systemic vascular resistance cause the central aortic pressure and left ventricular (LV) load to rise, which, in turn, requires greater contractile force to maintain cardiac output and forward flow. This manifests as an increase in both the rate and magnitude of LV pressure (dp/dt) which, in the absence of cardiac dysfunction, imparts greater mechanical stress and shear force on the aorta. However, when underlying LV remodeling or overt cardiac dysfunction are present, the ventricle may be too weak to generate sufficient pumping force (systolic dysfunction) or too stiff to accommodate the necessary increase in LV pressure (diastolic dysfunction). Either may produce a relative decrease in preload recruitable stroke work, and thus stroke volume, precipitating back-flow of fluid into the lungs and rapid onset of acute heart failure. This has often been termed “flash pulmonary edema”.  

### Table 3. Causes of secondary hypertension

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Coarctation of the aorta</td>
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<tr>
<td>Cushing’s syndrome and other glucocorticoid excess states</td>
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<tr>
<td>Sympathomimetic drug use</td>
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<tr>
<td>Pheochromocytoma</td>
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<tr>
<td>Hyperaldosteronism and other mineralocorticoid excess states</td>
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<tr>
<td>Renovascular cause</td>
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<tr>
<td>Sleep apnea</td>
</tr>
<tr>
<td>Thyroid or parathyroid disease</td>
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</table>

**PATIENT EVALUATION:**

**General Approach**

Hypertensive emergencies are generally accompanied by symptoms related to the target-organ that is acutely involved. Focal neurological deficit or altered mentation point to brain injury while chest pain or shortness of breath are indicative of cardiac or vascular involvement. Though frequently encountered, and potentially worrisome depending on the scenario, symptoms such as headache or dizziness do not, in and of themselves, serve as criterion from which a diagnosis of hypertensive emergency can be established. Retinal or kidney involvement tends to be more cryptic but can, depending on the degree of associated papilledema, uremia, acidosis or hyperkalemia, present with defining clinical features such as blurred vision, obtundation, Kussmaul respirations, palpitations or ventricular dysrhythmias.

The work-up of a hypertensive emergency should be guided by symptoms and signs identifiable on clinical examination which should include funduscoppy. Depending on the case, the evaluation of HTN can involve the use of one or more of the following modalities: plain film radiography (chest x-ray), computed tomography, magnetic resonance imaging, electrocardiography, or echocardiography. Laboratory testing for renal dysfunction including a urinalysis and a basic metabolic panel is recommended for most patients regardless of their presentation. More sensitive novel biomarkers of acute renal injury such as cystatin-c, neutrophil-gelatinase associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1) may be incorporated in the future.

**Asymptomatic Hypertension**

The necessity for testing is to identify occult target-organ damage in patients who have profound yet asymptomatic HTN is not clear. In a recent multicenter study of 109 such patients, clinically meaningful unanticipated test abnormalities were detected in only 6%. None of these tests were felt by the treating physician to be definitively attributable to HTN. None of these tests were felt by the treating physician to be definitively attributable to HTN. Chest x-ray and echocardiography in particular have poor sensitivity for detection of subclinical cardiac disease, especially LV hypertrophy, and a low likelihood of altering clinical management. Investigation of other approaches to detect clinically silent target-organ cardiac damage such as measurement of serum natriuretic peptide (NP) biomarkers such b-type NP (BNP) and n-terminal pro-BNP (NT-proBNP) concentration have yielded conflicting results. Based on
the findings of a recent study using echocardiography, the prevalence of subclinical target-organ cardiac damage among those with asymptomatic, severely elevated BP in the ED may be far greater (approximately ~75%) than previously thought. Such data highlight the underlying risk for pressure-mediated consequences of poor BP control among these patients and suggest a potential benefit from more extensive screening particularly in the outpatient setting.

While the current approach to routine testing may not impact acute care in asymptomatic hypertensives, there is value in knowing information such as baseline renal function and electrolyte levels prior to initiation of antihypertensive therapy. Accordingly, the JNC 7 recommends that a basic metabolic panel be obtained before prescribing oral BP lowering medications. It is most appropriate to have such medications initiated or restarted by the patient’s primary care physician. When follow-up cannot be ensured, this responsibility may fall on the ED provider. Based on existing evidence, first-line therapy for nearly all hypertensive individuals should involve the use of thiazide or thiazide-like diuretics like chlorothalidone with the addition of a second agent, usually an angiotensin converting enzyme inhibitor (ACE-I) or a calcium channel blocker, if the patient has chronic HTN which is poorly controlled on monotherapy.

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### MANAGEMENT:

**Antihypertensive Therapy**

While some oral or sublingual medications have a relatively quick onset of action, a more predictable, controlled antihypertensive effect can be achieved with parenteral agents making them preferable in the setting of a true hypertensive emergency. According to data from the Study of the Treatment of Acute hyperTension (STAT) registry, labetalol is the most common IV antihypertensive medication used for management of severely elevated BP, defined in the registry as BP > 180/110 mm Hg, and nitroglycerin is the infusion used most frequently. Direct comparison data are scant with regard to the relative efficacy of differing agents. A Cochrane Review of 15 randomized controlled trials (n = 869) involving 7 different drug classes including nitrates, ACE-I, diuretics, calcium channel blockers, α₁-adrenergic antagonists, direct vasodilators and dopamine agonists, concluded that despite minor differences in the degree of BP lowering with one antihypertensive class versus another, there was insufficient evidence to determine which agent is most effective at reducing morbidity or mortality. More recent data from The ECLIPSE (Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events) trial, which compared clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine in 1512 cardiac surgery patients with acute HTN and the CLUE (Evaluation of Intravenous nCardipine and Labetalol Use in the Emergency Department) study, which included 226 ED patients with severely elevated BP, suggest superiority but within class equivalence of IV dihydropyridine calcium channel blockers for BP reduction, such as more rapid lowering and greater time spent within prespecified target range, versus alternative therapy. Although mortality was also slightly lower in ECLIPSE with use of clevidipine compared to sodium nitroprusside only, generalizability of this finding is limited by virtue of the select patient population enrolled. Because the focus of the CLUE study was immediate BP lowering effects, outcomes beyond 30 minutes were not assessed. Consequently, the “hard” clinical meaning of observed group-wise differences in BP reduction is unclear.

Given existing data limitations, deciding which parenteral medication is best for an individual patient can be challenging. Understanding the pharmacology of differing therapeutic options can facilitate utilization, enhance the ability to direct intervention towards the appropriate precipitant, and help avoid potentially harmful application. As shown in the following equation, mean arterial pressure (MAP) can be reduced by lowering any of the following parameters: systemic vascular resistance (SVR) which stems largely from regulation of vasogenic tone in the arterioles, cardiac output (CO) which is the pumping force of the heart, or central venous pressure (CVP) which represents intravascular volume and, more roughly, hydrostatic force in the circulatory system. As with most physiology, these parameters do not work in isolation and perturbations in one may affect the other. For example reducing CVP causes, by the Frank-Starling principle, a decrease in CO:

\[
\text{MAP} = (\text{CO} \times \text{SVR}) + \text{CVP}
\]
Most intravenous (IV) antihypertensive agents exert their effect directly either through receptor-mediated activation or inhibition or indirectly through a decrease in production or release of endogenous vasoconstrictors. As shown in Table 4, the specific hemodynamic response is a function of the pathway being interrupted. For the most part, all IV antihypertensives produce some decrease in SVR. The magnitude of BP reduction is largely a reflection of the mechanism of action. Intrinsic dose response relationships, which often change with aging, are important to consider when using any agent clinically.42

Specific Indications

In clinical practice, antihypertensive therapy is often administered simply to control elevated BP with clinicians using medications with which they are most familiar. For treatment of a true hypertensive emergency however, therapeutic intervention is best directed towards the precipitant of specific target-organ dysfunction and the acute consequences of elevated BP rather than the BP itself. As indicated in Table 2, the vast majority of hypertensive emergencies involve the brain or heart and treatment goals should reflect the specific problems caused by high pressures. For instance, in acute coronary syndromes complicated by HTN, the primary goal beyond reperfusion is a reduction in cardiac work-load and an increase in coronary artery perfusion. Based on respective pharmacodynamic profiles and existing evidence,42,43 specific agents can be aligned with indication driven goals to develop an approach to management which is likely to yield optimal outcomes (Table 5). While few absolute contraindications exist, nitric oxide donors do cause greater reduction in systemic (vs. cerebral) vascular resistance resulting in relatively greater intracranial pressure and the potential for shunting of blood flow to the peripheral circulation.44 Similar effects may also occur with hydralazine and both classes should be used with caution or avoided in neurologic hypertensive emergencies.45,46

Blood Pressure Goals

The long-standing approach to antihypertensive medication use is to target a maximal reduction in MAP of 25% within the first hour and a goal BP of 160/100 mm Hg by 2-6 hours.3,16 This treatment is based on existing understanding of the cerebral pressure-flow autoregulation curve, which shifts to the right in chronic HTN. An excessive decrease in BP may lead to a precipitous decline in cerebral blood flow.19 Given the heterogeneity of acute target-organ dysfunction, the use of as a singular goal for BP control in all hypertensive emergencies makes little physiologic sense. This is particularly true for conditions such as aortic dissection, where more aggressive targets such as a systolic BP < 110 mm Hg have been recommended to decrease ongoing injury and reduce the likelihood of perioperative adverse events.47 Similarly, reductions in MAP which exceed 30% have been associated with more rapid symptom resolution and improved outcomes in acute
Table 5. Indications, treatment goals and recommended agents

<table>
<thead>
<tr>
<th>Indication</th>
<th>Goals of Treatment</th>
<th>Optimal Agents</th>
<th>Caveses</th>
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<tbody>
<tr>
<td>Acute coronary syndromes</td>
<td>Diminish cardiac workload and improve coronary artery perfusion</td>
<td>Nitroglycerin, esmolol, labetalol, metoprolol, nicardipine</td>
<td>Routine use of IV β-blockers controllable</td>
</tr>
<tr>
<td>Acute heart failure syndromes</td>
<td>Reduce importance to forward flow and diminish cardiac workload</td>
<td>Nitroglycerin, sodium nitroprusside, nitroprusside, osmolol, furosemide</td>
<td>Induction of or non-invasive ventilatory support decreases preload and may drop BP</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Reduce shear force and dympathrosis</td>
<td>Labetalol, esmolol, lisinopril, nicardipine, or clonidine</td>
<td>Avoid β-blocker if aortic regurgitation is present</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>Reduce hemoragic conversion and edema while avoiding regional hypoperfusion</td>
<td>Labetalol, nicardipine, esmolol</td>
<td>Acute BP reduction indicated only with planned fibrinolytic administration or additional acute tangle-organ dysfunction</td>
</tr>
<tr>
<td>Acute intracerebral hemorrhage</td>
<td>Reduce hematoma expansion and perihematoma edema</td>
<td>Labetalol, nicardipine, esmolol</td>
<td>BP may decrease with pain management allows clonidine currently under investigation</td>
</tr>
<tr>
<td>Hypertensive encephalopathy*</td>
<td>Decrease intracranial pressure</td>
<td>Labetalol, nicardipine, esmolol</td>
<td>Consider other causes of altered mental status in this work-up</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Decrease pressure in renal parenchyma</td>
<td>Furosemide, sodium nitroprusside, nicardipine, clonidine</td>
<td>Avoid angiotensin converting enzyme inhibitors and diuretics</td>
</tr>
<tr>
<td>Edemaema</td>
<td>Decrease intracranial pressure while maintaining placental perfusion</td>
<td>Hydralazine, labetalol, nicardipine</td>
<td>Administer IV magnesium in all cases; emergent C-section is definitive treatment</td>
</tr>
<tr>
<td>Sympathetic crisis</td>
<td>Reduce U-adrenergic receptor mediated vasoconstriction</td>
<td>Phentolamine, nitroglycerin, nicardipine, clonidine, furosemide</td>
<td>Benzodiazepines useful when caused by cocaine or amphetamines; β-blocker monotherapy contraincated</td>
</tr>
</tbody>
</table>

* Nitric oxide donors and hydralazine should be avoided with these indications

Advancing the Standard of Care: Cardiovascular and Neurovascular Emergencies

Heart failure patients with a hypertensive phenotype.48,49 A recent subanalysis of 302 patients with acute heart failure in the STAT registry found that adverse events were increased when systolic BP was lowered beyond 120 mm Hg within 12 hours. This underscores the need for continued vigilance when managing this condition.50

Understanding the importance of BP goals may be most critical when treating neurologic hypertensive emergencies. This is evident on review of the current American Heart Association/American Stroke Association (AHA/ASA) guidelines for acute ischemic stroke, which call for a BP reduction to < 185/110 mm Hg when thrombolysis is planned. Otherwise, antihypertensive therapy is only indicated when BP is markedly elevated (> 220/120 mm Hg) with a goal to decrease by approximately 15% at 24 hours post-onset.51 This is supported by a meta-regression of BP control in stroke which suggests an association between large falls or increases in BP and worse outcome and modest reductions with a decrease in death and/or dependency.52 Updated in 2010, the AHA/ASA guidelines for acute intracerebral hemorrhage state that “aggressive” reduction is warranted when systolic BP is > 200 mm Hg or MAP is > 150 mm Hg and more modest decreases are indicated with target BP 160/90 mm Hg or MAP 110 mm Hg when lesser elevations, defined as systolic BP > 180 mm Hg or MAP > 130 mm Hg, are present.53 The persistent BP elevation in the setting of acute intracerebral hemorrhage is associated with hematoma expansion and worse outcomes prompted the recent study of the target and timing of antihypertensive therapy. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT; n = 404) and the Antihypertensive Treatment of Acute Cerebral Hemorrhage study (ATACH; n = 60) compared differing BP goals, finding a strong signal that earlier intervention with lower BP targets (systolic BP approximately 140 mm Hg) may attenuate hematoma expansion without an excess of adverse events.54-57 To achieve such targets, nicardipine may be more effective than other agents including labetalol.58

Disposition

With little exception, patients with hypertensive emergency should be admitted to a monitored setting. By virtue of the presenting clinical picture and the corresponding use of IV antihypertensive medications, some of which can produce precipitous drops in blood pressure, many will require on-going treatment in a step-down or intensive care unit. In certain circumstances, such as chest pain with elevated BP or acute deterioration of chronic kidney disease, short-term management in an observation unit may be appropriate. This presumes that timely reassessment and expeditious completion of the diagnostic work-up can be assured in this setting.59

Prognosis

Outcomes associated with a given hypertensive emergency are largely a function of underlying target-organ damage. Data from STAT suggest that severe HTN is a high-risk condition with in-hospital and 30-day mortality rates of 6.9% and 11%, respectively, and a 90-day readmission rate of nearly 40%.60 When associated with moderate to severe acute kidney injury, mortality is even greater (odds ratio = 1.05; p=0.03 per 10-mL/min decline).60
Conclusion

Severe BP elevations in the ED are common. Differentiating a true hypertensive emergency from poorly controlled chronic HTN is critical to enable appropriate application of resources. When indicated, therapeutic intervention should be driven by condition-specific goals using agents appropriate for the disease manifestations. Understanding the pharmacology of antihypertensive medications can facilitate management and better prepare the emergency physician to provide care for this important group of patients.

References

14. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967;202:1028-34.


