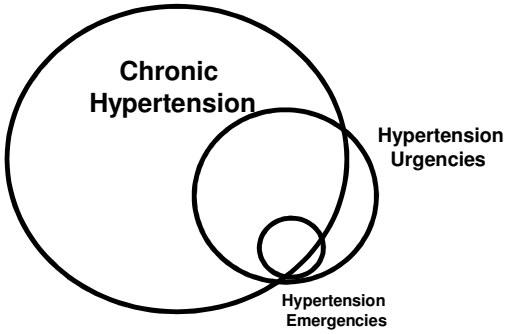
Current State of Hypertensive Crisis Management

- Hypertensive crises are among the most misunderstood acute medical conditions
- Delays in initiating therapy can cause severe complications
- Overzealous therapy can be equally damaging
- Understanding the pathophysiology involved in hypertensive crises helps in deciding optimal treatment strategies

Varon J, Marik PE. *Chest.* 2000;118:214-227.
Epstein M. *Clin Cornerstone.* 1999;2:41-54.

Hypertension Emergencies in context



Severe hypertension is relatively common

Patient and visit characteristics	Number of visits in thousands	Total	Percent distribution					
			Low	Normal	Mildly high	Moderately high	Severely high	Blank
All visits 18 years and over[2]	92,895	100.0	6.0	14.6	33.5	25.8	16.2	3.9
Age								
18–24 years				22.8	43			
25–44 years				17.3	37			
45–64 years				10.4	29			
65–74 years				9.3	23			
75 years and over				6.9	23			
Sex								
Female				16.7	33			
Male				11.8	33			
Race[3]								
White	67,183	100.0	6.2	14.1	34.2	26.1	15.6	3.7
Black	22,558	100.0	5.2	15.8	31.6	24.9	17.9	4.6
Asian	1,800	100.0	8.5	14.7	31.6	23.6	18.4	3.2
Other	1,354	100.0	6.7	14.8	33.3	30.0	12.5	*
Ethnicity								
Hispanic or Latino	10,696	100.0	5.9	18.0	34.4	24.4	12.6	4.7
Not Hispanic or Latino	82,199	100.0	6.0	14.1	33.4	26.0	16.6	3.8

There are ~100,000 ER visits each year for hypertension

~15,000 of those visits are for severely high BP

Pitts et al. Natl Health Stat Report 2008;7:1-38.

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Follow up

Terminology and Definitions (JNC 7)

Urgency **Emergency**

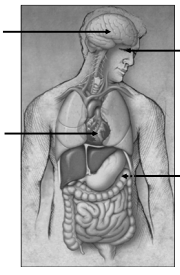
The diagnosis of hypertensive emergencies depends on the clinical manifestations rather than only on the absolute level of the blood pressure.

End-Organ Damage Characterizes Hypertensive Emergencies

Brain
Hypertensive encephalopathy
Stroke

Retina
Hemorrhages
Exudates
Papilledema

Cardiovascular System
Unstable angina
Acute heart failure
Acute myocardial infarction
Aortic dissection



Kidney
Acute renal failure

Adapted from Varon J, Marik PE. *Chest.* 2000;118:214-227.

Hypertensive Encephalopathy

PRES:
Posterior reversible encephalopathy syndrome

Typically symmetrical white matter edema in the posterior cerebral hemispheres

What the primary care clinician needs to know

How do you differentiate a hypertensive URGENCY from a hypertensive *EMERGENCY*?

Hypertensive crisis

- You will almost certainly see a hypertensive urgency in your career
- You will also likely see a hypertensive emergency
  - Only occur in 1-2% of the hypertensive population
  - But, there are 50 million hypertensive Americans
  - 500,000 hypertensive emergencies/year
- Higher in the elderly and African Americans
- Incidence is twice as high in men as compared to women

Hypertensive Urgencies / Emergencies:

- Classification / Definition
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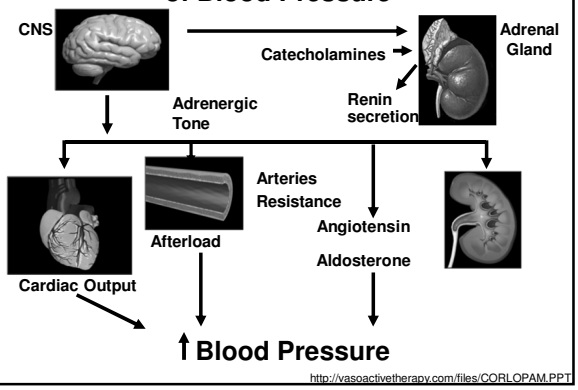
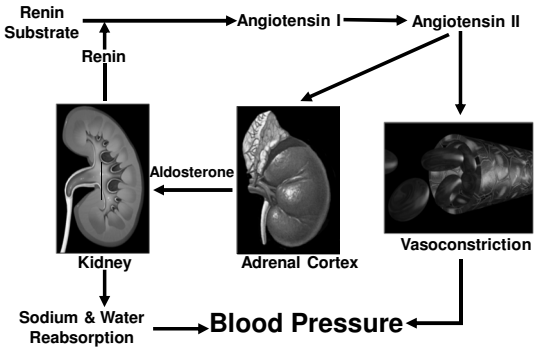
Sympathetic Nervous System Regulation of Blood Pressure



http://vasoactivetherapy.com/files/CORLOPAM.PPT

Renin-Angiotensin-Aldosterone Regulation of Blood Pressure



Almost all cases of Hypertension can be explained by:

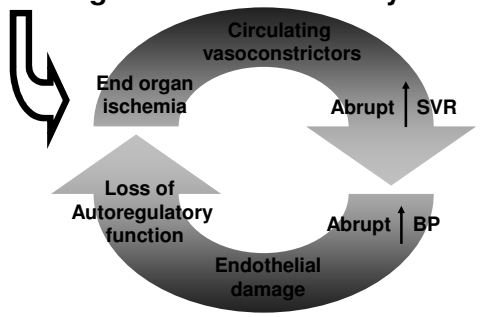
- Sodium excess
- Extracellular volume expansion
- Sympathetic overactivation

Too Much Sodium (Salt)

Too Much Water

Too Much Sympathetic Activity

Pathophysiology of Hypertensive Emergencies: a Vicious Cycle



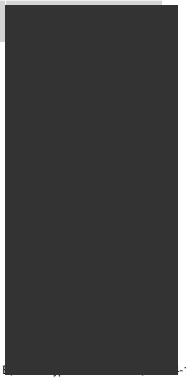
Ault NJ, et al. *Am J Emerg Med.* 1985;3(6 suppl):10-15. 2. Wallach R, et al. *Am J Cardiol.* 1980;46:559-565. Varon J, et al. *Chest.* 2000;118:214-227. 4. Kincaid-Smith P. *J Hypertens.* 1991;9:893-899.

What the primary care clinician needs to know

How do patients with hypertensive URGENCIES and hypertensive *EMERGENCIES* present?

Signs and Symptoms

Signs and Symptoms	HTN Urgency (%)
Headache	22
Epistaxis	17
Chest Pain	9
Dyspnea	9
Faintness	10
Agitation	10
Neurologic Deficit	3
Vomiting	2
Arrhythmia	6



Zampaglione [illegible] -147.

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Outcomes

Goals of evaluation are to determine etiology, and rapidly assess for end organ damage

Initial Evaluation

- Symptoms
- Medical History
  - Episodic palpitations and perspiration?
- Medications
  - MAO inhibitors
  - Clonidine
- Social History
  - Recreational Drugs
    - Amphetamines
    - Cocaine
    - Phencyclidine

Physical Exam

- Blood pressures must be taken in both arms
  - If the cuff is too small, the BP will be falsely elevated
  - If the cuff is too low (below the level of the heart), the BP will be falsely elevated
- Pulses should be checked in upper and lower extremities
- Neuro exam
- Cardiac exam
- Pulmonary exam
- **Ocular exam**: only happens in 13% of pts

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Outcomes

Management of Hypertensive Urgencies

Severely Increased Blood Pressure in the Emergency Department

Philip H. Shayne, MD
Stephen R. Pitts, MD, MPH

From the Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA.

Editor's note: This artic... tinues a series of specia... tributions addressing state-of-the-art techniq... ics, or concepts. State-of-the-art articles will be featured in Annals on a regular basis in the next several volumes.

See commentary, p. 530.

Patients with severely increased blood pressure often present to the emergency department. Emergency physicians evaluate and treat hypertension in various contexts, ranging from the compliant patient with well-controlled blood pressure to the asymptomatic patient with increased blood pressure to the critically ill patient with increased blood pressure and acute target-organ deterioration. Despite extensive ... spectrum of disease, from the asymptomatic to critically ill patient, and the dilemma it creates for the emergency physician in deciding how and when in the process to intervene.

"There is no clear consensus on the acute management"

Shayne and Pitts. Ann Emerg Med. 2003;41:513-29.

Pharmacological interventions for hypertensive emergencies

Marco I Perez[1], Vijaya M Musini[1], James M Wright[1]

Does anti-hypertensive drug therapy as compared to placebo or no treatment affect mortality and morbidity in patients with a hypertensive emergency?

Does one first-line antihypertensive drug class offer a therapeutic advantage, in terms of mortality and morbidity, over another in patients with a hypertensive emergency?

Main results

Fifteen randomized controlled trials (representing 869 patients) met the inclusion criteria. Two trials included a placebo arm. All studies (except one) were open-label trials. Seven drug classes were evaluated in those trials: nitrates (9 trials), ACE-inhibitors (7), diuretics (3), calcium channel blockers (6), alpha-1 adrenergic antagonists (4), direct vasodilators (2) and dopamine agonists (1).

Authors' conclusions

There is no RCT ev... emergencies. Further... mortality and morbid... drug is compared to a... initial and longer term mortality and morbidity outcomes.

"There is insufficient RCT evidence to determine which drug or drug class is most efffective in reducing mortality and morbidity."

Perez et al. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD003653.

What the primary care clinician needs to know

What are appropriate therapies to manage a hypertensive URGENCY?

For treatment of hypertension urgencies you want:

- Oral medication
- Long acting
- Lowers blood pressure effectively
- Has few side effects
- Can be transitioned to chronic therapy
- NO rebound
- NO common contraindications
- Improves outcomes

Oral medication choices for hypertensive urgency

- Appropriate choices
  - ACE-inhibitors
  - Angiotensin receptor blockers (ARBs)
  - Calcium channel blockers
  - Thiazide-type diuretics
- ***LESS APPROPRIATE*** choices
  - Labetalol (very effective but requires multiple daily doses)
  - Hydralazine (reflex tachycardia, multiple daily doses)
  - Beta blockers (less BP lowering and clinical benefit)
  - Alpha blockers (less clinical benefit)
  - Clonidine (overshoot, rebound hypertension, outcomes)

Clonidine

- MOA is suppression of sympathetic outflow from CNS
- If clonidine is abruptly d/c'd, rebound HTN can occur
  - This happens because of abrupt return of sympathetic outflow (mimics a sympathetic crisis)
- Clonidine withdrawal is often more severe in patients who are also taking a ß-blocker
  - ß-blockers inhibit beta-mediated vasodilation and leave unopposed α-medicated vasoconstriction
- So stop ß-blockers before Clonidine
- Clonidine weaning should occur over WEEKS
- If rebound hypertension occurs, treatment is to re-start clonidine and wean more slowly

Clonidine can "overshoot"

- A 1983 paper reported:
- "In 20 patients with severe hypertension, rapid oral clonidine titration was employed…"
- " Baseline BP was 212 ± 7 / 134 ± 3 mm Hg and decreased to 151 ± 5 / 104 ± 3 mm Hg."
- "The mean dose was 0.32 ±0.02 mg, and mean response time 1.8 ±0.2 hours…"
- "Side effects were minimal, except for ***one patient who died of a cerebral infarct, which developed after the blood pressure was lowered with clonidine."***

Use of Oral Clonidine for Rapid Titration of Blood Pressure in Severe Hypertension. Samuel Spitalewitz, Jerome G. Porush, Chika Oguagha. *Chest, Volume 83, Issue 2, February 1983, Pages 404-407*

What the primary care clinician needs to know

What is the appropriate follow up for a patient with a hypertensive URGENCY?

Follow up after outpatient management of a hypertensive urgency

- Administer or prescribe antihypertensive therapy
- Prescribe sufficient medication to last until f/u
- Follow up appointment for 1 day to 1 week later
- Very clear instructions for symptoms that require prompt medical evaluation
  - Evidence of end organ damage
  - Side effects of medication

Patients with hypertensive urgency respond to "rest" and meds

- 549 patients admitted to an ED for HTN (avg BP 192/106)
- All patients given a 30-minute rest period
  - A satisfactory BP response to rest was observed in 31.9% of population (BP < 180/110)
- Patients who ***did not*** respond to rest were randomly assigned to: perindopril, amlodipine, or labetalol
- 79.1% had a satisfactory BP response to medication
  - At 2 hours, NO difference in BP response by drug
- AUTHORS CONCLUSIONS: Rest as an initial step can be effective and safe for hypertensive urgencies

EARLY FOLLOW UP IS ESSENTIAL!

Grassi et al. J Clin Hypertens 2008;10:662–7.

Patients with hypertensive urgency have low short term event rates

- Retrospective review of all patients seen at a Cleveland Clinic outpatient facility from 2008-2013.
- 4.6% of visits had hypertensive urgency.
- Mean age - 63.1; 57.7% women; 76.0% white. Mean BMI - 31.3; Mean BP - 183/96 mm Hg
- 0.7% were sent to the hospital; the others sent home.
- Fewer than 1% of patients (0.9%) had a major adverse cardiovascular event in the next 6 months.
- Rates were not different for those referred to the hospital vs. those sent home

Patel KK et. al. *JAMA Intern Med.* published on line June 13, 2016

Patients with hypertensive urgency have higher LONG - term event rates

- 206,147 ED visits for HTN in Ontario, Canada, from 2002 to 2012.
- Median age 64 years, 81.4% had known hypertension.
- ED visits for HTN increased from 15,793 per year in 2002 to 25,950 per year in 2012 (a 64.3% increase)
- The most frequent causes for hospital admission were stroke (5.3%), renal failure (5.2%) and CHF (3.1%).
- Mortality was 0.17% at 7 days, 0.43% at 30 days, 0.85% at 90 days, 2.5% at 1 year at 4.4% at 2 years

Masood S, et al. *Ann Emerg Med.* 2016;doi:10.1016/j.annemergmed.2016.04.060.

Elderly woman with hypertension

- 78 year old woman with HTN
- During a routine visit BP = 205 / 75
- No complaints except "not feeling right"; fundi could not be seen due to cataracts but otherwise normal exam
- Admits to running out of her BP meds
- We placed her in a quiet room and administered her usual BP medications
- 2 hours later BP 165/70; she felt well
- Sent home on usual meds with home health and follow up visit in 1 week

66 year old man with HTN prior NSTEMI

- 66 year old male who is s/p NSTEMI
- Cardiac risk factors include hypertension, obesity and smoking
- Went to urgent care when he "felt ill"
- BP 200/110 but decreased to 170/90
- Ruled out for MI then sent home and told to speak to PCP at next visit
- PCP and cardiologist never notified
- 2 months later wife called cardiologist when patient was 'dragging his left leg'
- Sent to ER where acute stroke was found

Management of Hypertensive Emergencies

39 year old man with chest pain and shortness of breath

Causes of hypertensive emergencies:

1. **Too much sodium**
2. **Too much water (missed HD)**
3. **Too much sympathetic activity (Methamphetamine use)**

What the primary care clinician needs to know

What is the appropriate management for a patient with a hypertensive *EMERGENCY*?

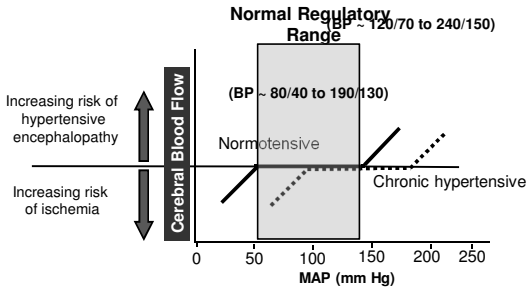
EMERGENCY DEPARTMENT
EMERGENCY DEPARTMENT
EMERGENCY DEPARTMENT

How Low Should You Go?

- Simple answer
  - 20-25% reduction in MAP within 1st hour
- Better answer
  - It really depends on clinical condition
    - Less aggressive with ischemic stroke
    - More aggressive with hemorrhagic stroke, acute HF and aortic dissection

Marik and Varon. Critical Care 2003, 7:374-84.

Cerebral Autoregulation Is Central to Treatment of Hypertensive Crises



Adapted from Varon J, Marik PE. *Chest*. 2000;118:214-227.

All blood pressure sensitive organs have some degree of autoregulation

Hypertensive Emergency: Goals of Therapy

- Immediate and *controlled* BP reduction
  - Reduce BP 20-25% within minutes to 1 hour
  - If patient is stable, reduce BP to160/100-110 mm Hg over the next 2-6 hours
  - If patient is stable, further gradual reductions toward normal BP over the next 24-48 hours
- More immediate BP reduction in certain cases in
  - e.g. Aortic dissection, hemorrhagic stroke
- Increased caution in acute ischemic stroke patients
  - In general, BP should not be lowered too aggressively

JMC 7. US Dept of HHS; NIH publication No. 03-5233; 2003:54. Adams HP, et al. *Stroke*. 2005;36:916-923.

Intensive Care Unit
Intensive Care Unit
Intensive Care Unit

Treatment Typically Parenteral (IV)

- Adrenergic receptor blockers
  - Esmolol (β_1)
  - Labetalol (α_1 and β)
  - Phentolamine (α_1)
  - Urapidil (α_1)
- Ca^{2+} channel blockers
  - Nicardipine
  - Clevidipine
- ACE inhibitors
  - Enalaprilat
- Nitric Oxide (NO) donors
  - Nitroprusside
  - Nitroglycerin
- Dopamine agonist
  - Fenoldopam
- Direct vasodilator
  - Hydralazine

Management of Sympathetic Crisis

- In a sympathetic crisis, Beta-blockers will result in unopposed alpha-adrenergic stimulation
- Thus, Beta blockers can
  - Paradoxically ***INCREASE*** blood pressure
  - Worsen coronary artery vasoconstriction
  - Decrease survival
- *In a sympathetic crisis, Avoid beta blockers (including non selective agents such as labetolol)*

Examples of sympathetic crises

- Pheochromocytoma
- Cocaine/amphetamines/OTC herbals (ephedra)
- Clonidine withdrawal
- Monoamine oxidase inhibitor + tyramine
  - Tyramine is found in many foods, and is a sympathomimetic (like amphetamine
  - Patients on MAOIs experience an exaggerated response to tyramine, resulting in prolonged and severe hypertension

Foods containing tyramine

- Beer
- Wine
- Aged cheeses
- Chocolate
- Coffee
- Pickled herring
- Citrus fruites
- Broad beans
- Chicken livers

Medications that interact w/ MAOI

- Meperidine
- Ephedrine
- TCAs
- Reserpine
- Dopamine
- Methyldopa
- Guanethidine

Hypertensive Urgencies / Emergencies:

- Classification / Definition
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- Outcomes

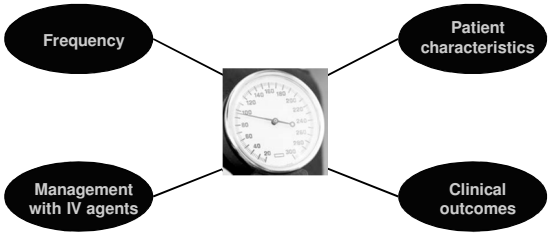
Follow-up care in hypertensive emergencies

- Goal: Transition to oral therapy as soon as possible
- Monitor carefully: Abrupt switch may result in ↑ BP
- Most patients may be discharged on oral medication within 24-72 hours
- Hospitalization for a hypertension crisis is a "teachable moment". This is an opportunity to stress improved BP control and medication adherence

Vidt DG. In: *Hypertension Primer.* In press.

STAT Registry: Addressing knowledge gaps in contemporary acute hypertension

Studying the Treatment of Acute Hypertension



Study Population

Patients	1,588
Age - median	58 (49 - 70)
Female sex	49%
Black race	56%
White race	34%
Qualifying BP	
Systolic	200 mm Hg (186 - 220)
Diastolic	110 mm Hg (93 - 123)
Length of stay	5 days (range 2 - 9)

Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

Medical History

Condition	*%*
Hypertension	**89**
Tobacco or alcohol use	38
Diabetes	35
Chronic kidney disease	31
End stage renal disease	11
Previous hospitalization for HTN	**27**
Neurological event	23
Drug abuse	15

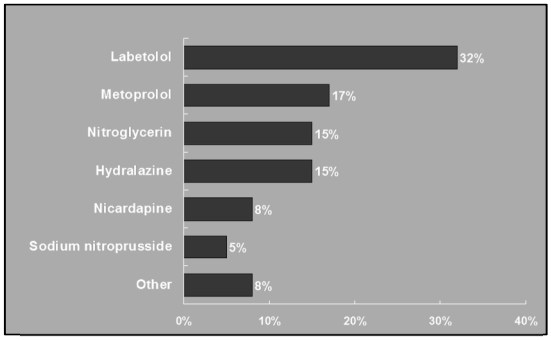
Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

Predisposing Factors Contributing to Hypertensive Event

Factors	***%***
Medication non-adherence	**25**
Chronic	16
Current	10
Missed or incomplete dialysis	3
Anxiety/psychosocial reaction	2
Drug abuse	11

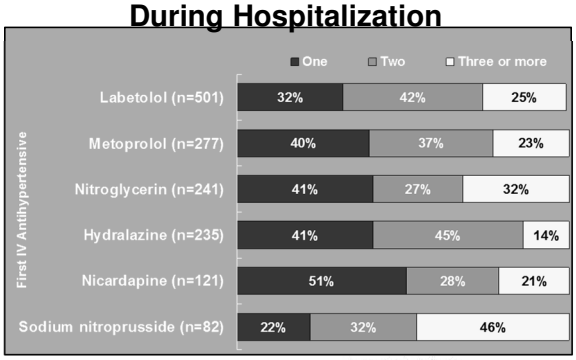
Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

First IV Antihypertensive used in this cohort



Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

Number of IV Antihypertensives During Hospitalization



Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

Short-Term (2 to 6 month) Outcomes for various clinical conditions

Acute Condition	Death	Rehospitalization
ACS[1,2,3]	5-7%	30%
CHF[4]	8.5%	26%
Severe Hypertension[5]	7-9%	37%

1. OASIS-5 *NEJM* 2006
2. GUSTO IIb *NEJM* 1996
3. GRACE *JAMA* 2007
4. IMPACT-HF *J Cardiac Failure* 2004
5. STAT Registry results

Am Heart J Volume 158, Issue 4, October 2009, Pages 599–606.e1

Summary

- Acute severe hypertension is
  - Associated with medical NONadherence
  - If a hypertensive EMERGENCY, requires ICU admission, IV drugs
  - Alarmingly low rates of follow-up
  - High mortality and morbidity, especially with new or worsening end-organ damage
- Major need to improve prevention and treatment of this important clinical condition