Management of Accelerated Hypertension

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Defining Hypertensive Crises

Different terminologies used interchangebly

- Severe Hypertension
- Accelerated Hypertension
- Malignant Hypertension
- Hypertensive Crisis

Hypertensive crisis

- It is a terminology for acute, severe elevations in BP
- It can present in two forms
  - Hypertensive urgency
  - Hypertensive emergency

- Systolic BP ≥ 180 mmHg OR
- Diastolic BP ≥ 120 mmHg
- ≥ 180/110 (NICE guidelines)
- ≥ 200/110 (BHS guidelines)

Hypertensive urgency

- BP is severely elevated (SBP ≥ 180 mmHg OR DBP ≥ 120 mmHg); but there is **NO** target organ damage

- Symptoms can be:
  - Severe headache
  - Shortness of breath
  - Nose bleeds
  - Severe anxiety

Hypertensive emergency

- BP is severely elevated (SBP ≥ 180 mmHg OR DBP ≥ 120 mmHg); complicated by evidence of impending or progressive target organ dysfunction

- Target organ dysfunction can be in these forms:
  - hypertensive encephalopathy
  - intracerebral hemorrhage
  - acute MI
  - acute left ventricular failure with pulmonary edema
  - unstable angina pectoris
  - Eclampsia
  - Aortic dissection

Malignant Hypertension

Hypertensive emergency leading to

- Papilloedema
- Encephalopathy

End-Organ Damage Characterizes Hypertensive Emergencies

Brain

Hypertensive encephalopathy

Stroke

Cardiovascular System

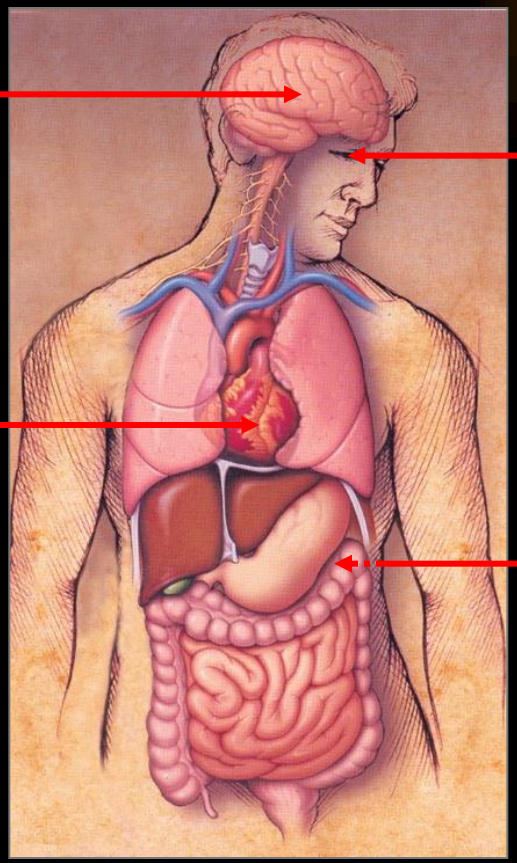
Unstable angina

Acute heart failure

Acute myocardial infarction

Acute aortic dissection

Dissecting aortic aneurysm



Retina

Hemorrhages

Exudates

Papilledema

Kidney

Hematuria

Proteinuria

Decreasing renal function

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

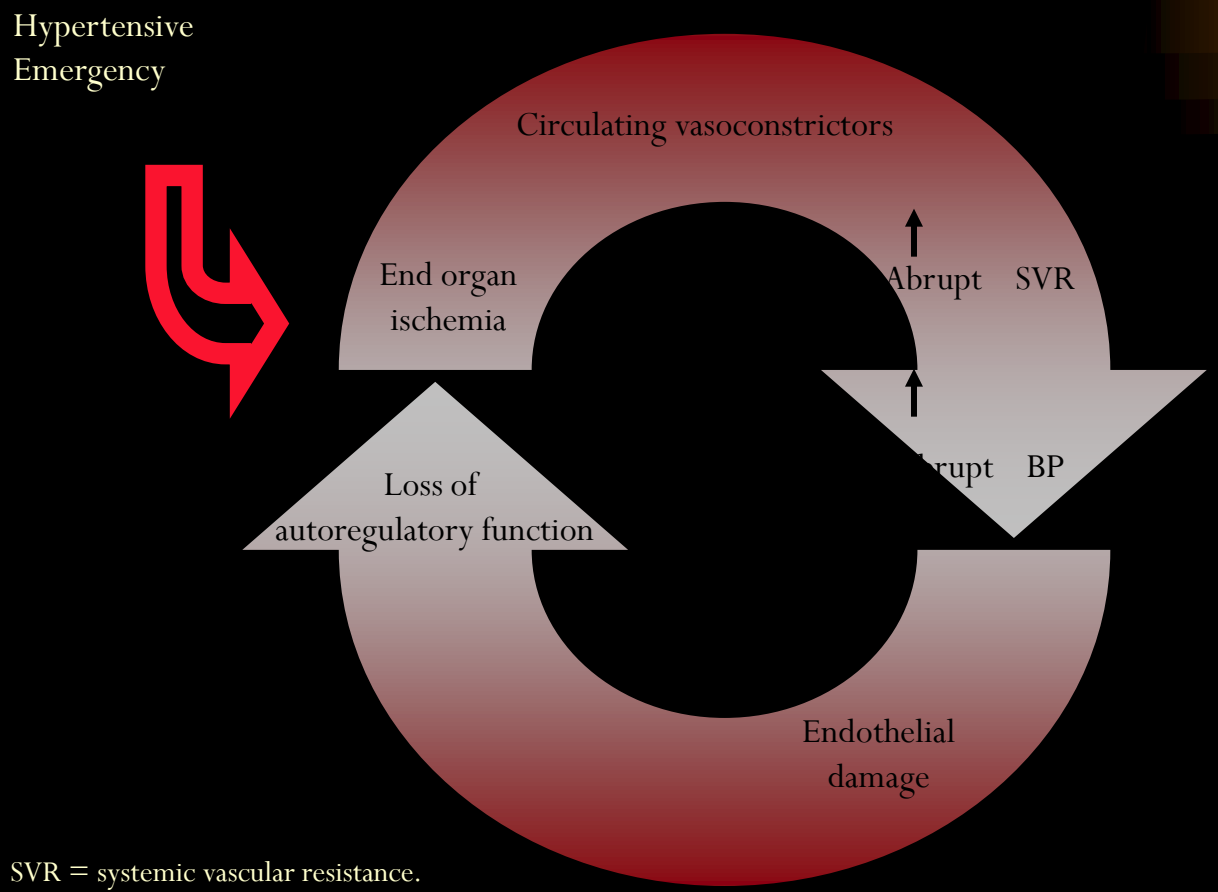
Major Risk Factors for Hypertensive Emergencies

- Antihypertensive therapy failing to provide adequate blood pressure control
- Failure to adhere to prescribed antihypertensive regimens
- Illicit drug use

Varon J, Marik PE. *Critical Care.* 2003;7:374-384.

Pathophysiologic Principles at Work in the Hypertensive Milieu

Pathophysiology of the Hypertensive Emergency[1-4]



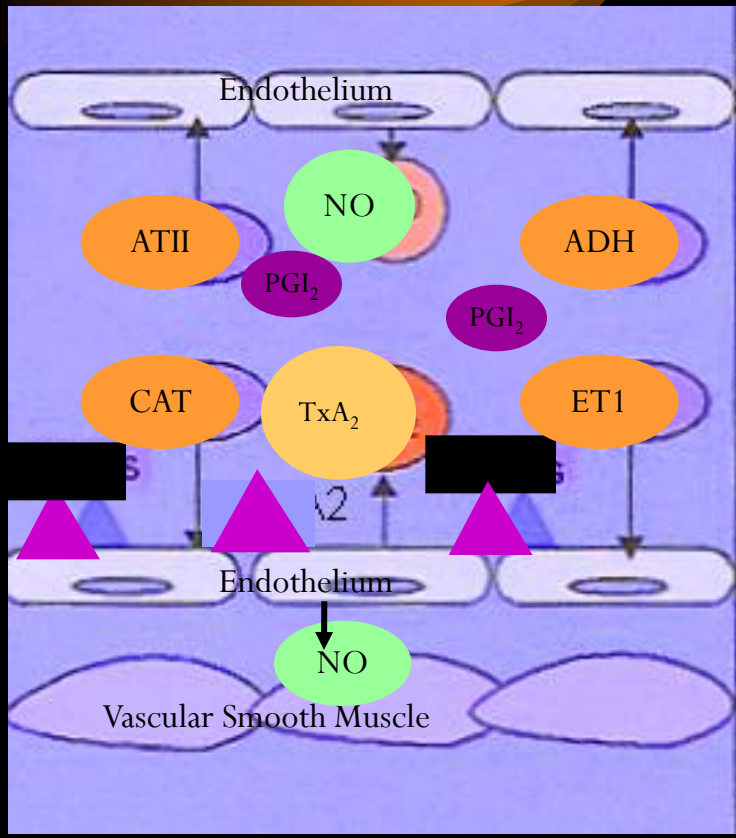
- Vasoconstriction, often with intravascular hypovolemia
  - Increased circulating catecholamines
  - Activation of renin-angiotensin-aldosterone system
  - Altered autoregulatory function

SVR = systemic vascular resistance.

1. 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.
3. Varon J, et al. *Chest.* 2000;118:214-227. 4. Kincaid-Smith P. *J Hypertens.* 1991;9:893-899.

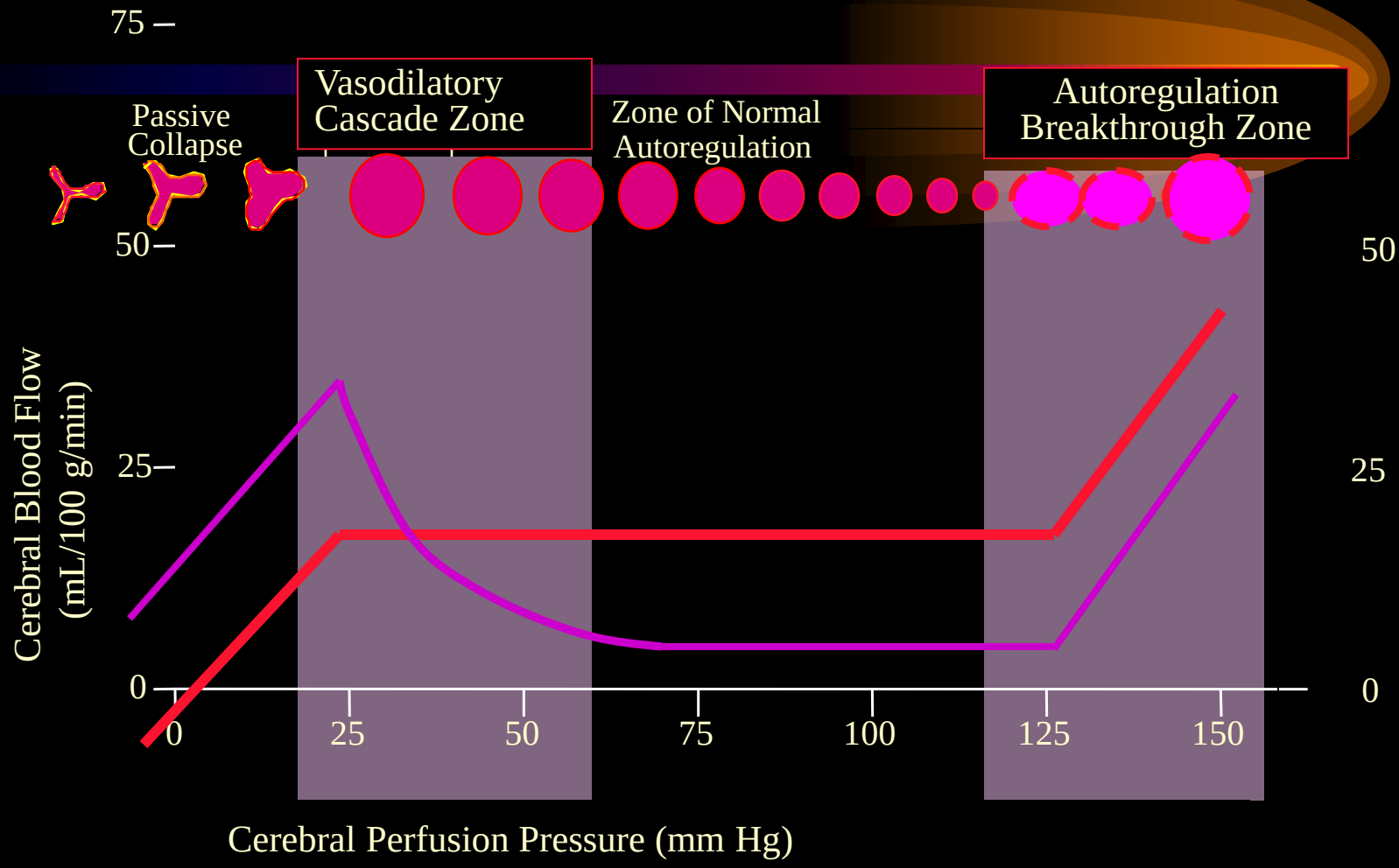
Endothelial/Vascular Smooth Muscle Interactions

- **Triggers of acute changes in vascular resistance**
  - Excess catecholamines (CAT)
  - Angiotensin II (ATII)
  - Vasopressin (ADH)
  - Aldosterone
  - Thromboxane (TxA_2)
  - Endothelin (ET1)
  - Low nitric oxide (NO) or prostaglandin (PGI_2)
- **Abrupt rise in BP**
  - Promotes expression of cellular adhesion molecules (CAMs)



Vaughan CJ, Delanty N. *Lancet*. 2000;356:411-417.

Hypertension Can Drive Elevated Intracranial Pressure



Courtesy of Stephan A. Mayer, MD.

Hypertensive Crisis: Basic Treatment Principles

- Place patient who is not in distress in a quiet room and reevaluate after an initial interview. In one study, 27% of patients with an initial DBP >130 mm Hg had their DBP fall below critical levels after relaxation without specific treatment.
- Consider the context of the elevated BP (eg, severe pain)
- Screen for end-organ damage- they usually require admission and rapid lowering of BP using iv meds.
- Suggested meds depend on the end-organ system damaged.
- Patients without evidence of end-organ effects may be discharged with oral medications and follow–up.
- It is a misconception that a patient should not be discharged from the ER with elevated BP.

Treatment of Hypertensive Emergency

- **JNC 7 -** mean arterial blood pressure (MAP) should be reduced by 25% or less within the first hour. Between hours 2 to 6, the target blood pressure is 160/100 to 160/110 mm Hg, followed by gradual normalization over 24 to 48 hours.

- The **2013 ESH/ESC guideline** recommends reducing blood pressure by less than 25% within the first hour and then subsequent cautious reduction thereafter.

Exceptions to the above recommendation :

- Patients with an ischaemic stroke
- Patients with aortic dissection
- Patients in whom BP needs to be lowered to enable the use of thrombolytic agents

Pharmacologic Profile of Commonly Administered IV Agents to Treat Hypertensive Emergencies

Properties of an Ideal Parenteral Antihypertensive Agent

- Rapid onset of action
- Predictable dose response
- Titratable to desired BP
- Minimal dosage adjustments
- Minimal adverse effects
- Not associated with coronary steal

Oparil S, et al. *Am J Hypertens*. 1999;12:653-664.

*Antihypertensive Agents Used in Hypertensive Crises**

- Clonidine
- Diazoxide
- Enalaprilat
- Esmolol
- Fenoldopam
- Hydralazine
- Labetalol
- Nicardipine
- Nifedipine
- Nitroglycerin
- Nitroprusside
- Phentolamine
- Trimethaphan

*Highlights denote more commonly used intravenous agents for hypertensive emergencies that are discussed in this presentation.

Enalaprilat

- ACE inhibitor[1]
- Onset of action: 15-30 minutes[2]
- Duration: 6-12 hours[2]
- Adverse effects: precipitous fall in pressure in high-renin states; variable response[2]
- Special indications/contraindications
  - Appropriate in acute left ventricular failure[2]
  - Contraindicated in acute myocardial infarction[2] or a history of angioedema[1]
  - Also contraindicated in MAP insufficient for renal perfusion, low cardiac output, volume depletion, renal vascular disease, and therapy with vasoconstrictor agents (eg, NSAIDs, cyclosporine A)

1. Vasotec® I.V. injection (enalaprilat). *Physician's Desk Reference*. 59th ed. Montvale, NJ: Thomson PDR; 2005:2170-2172. Enalaprit IV prescribing informatio n.

2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Dept of HHS; NIH publication No. 04-5230; 2004:55.

Esmolol

- $Beta_1$-blocker[1]
- Onset of action: 1-2 minutes[2]
- Duration: 10-30 minutes per bolus—may necessitate use of multiple boluses[2]
- Adverse effects: hypotension, nausea, asthma, first-degree heart block, and heart failure[2]
- Special indications/contraindications
  - Appropriate in aortic dissection and perioperative management[2]; supraventricular tachycardia, intraoperative and postoperative tachycardia and/or hypertension[1]
  - Contraindicated in sinus bradycardia, heart block greater than first degree, and cardiogenic shock or overt heart failure[1]
  - Use with caution in bronchospastic diseases, since $beta_1$ selectivity is not absolute[1]

1. Brevibloc injection (esmolol hydrochloride). *Physician's Desk Reference.* 59th ed. Montvale, NJ: Thomson PDR; 2005:804-808.

2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Dept of HHS; NIH publication No. 04-5230; 2004:55.

Labetalol

- Combined nonselective beta-blocker and alpha$_1$-blocker[1]
  - Beta-blockade is 7 times greater than alpha$_1$-blockade with IV administration[1]
  - Not associated with decreased cardiac output seen with pure beta-blockers[2]
- Onset of action: 5-10 minutes per bolus—may necessitate use of multiple boluses[2,3]
- Duration: 3-6 hours[3]
- Adverse effects: vomiting, brochoconstriction, dizziness, nausea, heart block, and orthostatic hypotension[3]
- Special indications/contraindications
  - Appropriate in most hypertensive emergencies except acute heart failure[3]
  - Contraindicated in bronchial asthma, severe bradycardia, heart block greater than first degree, overt cardiac failure, and cardiogenic shock[1]

3. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Dept of HHS; NIH publication No. 04-5230; 2004:55.

Nitroprusside

- Vasodilator—venous and arterial
- Onset of action: immediate
- Duration: 1-2 minutes
- Adverse effects: nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide toxicity
- Special indications/contraindications
  - Appropriate for most hypertensive emergencies
  - **Use with caution with high ICP or renal/hepatic dysfunction**
- Usually requires direct artery pressure monitoring

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Dept of HHS; NIH publication No. 04-5230; 2004:55.

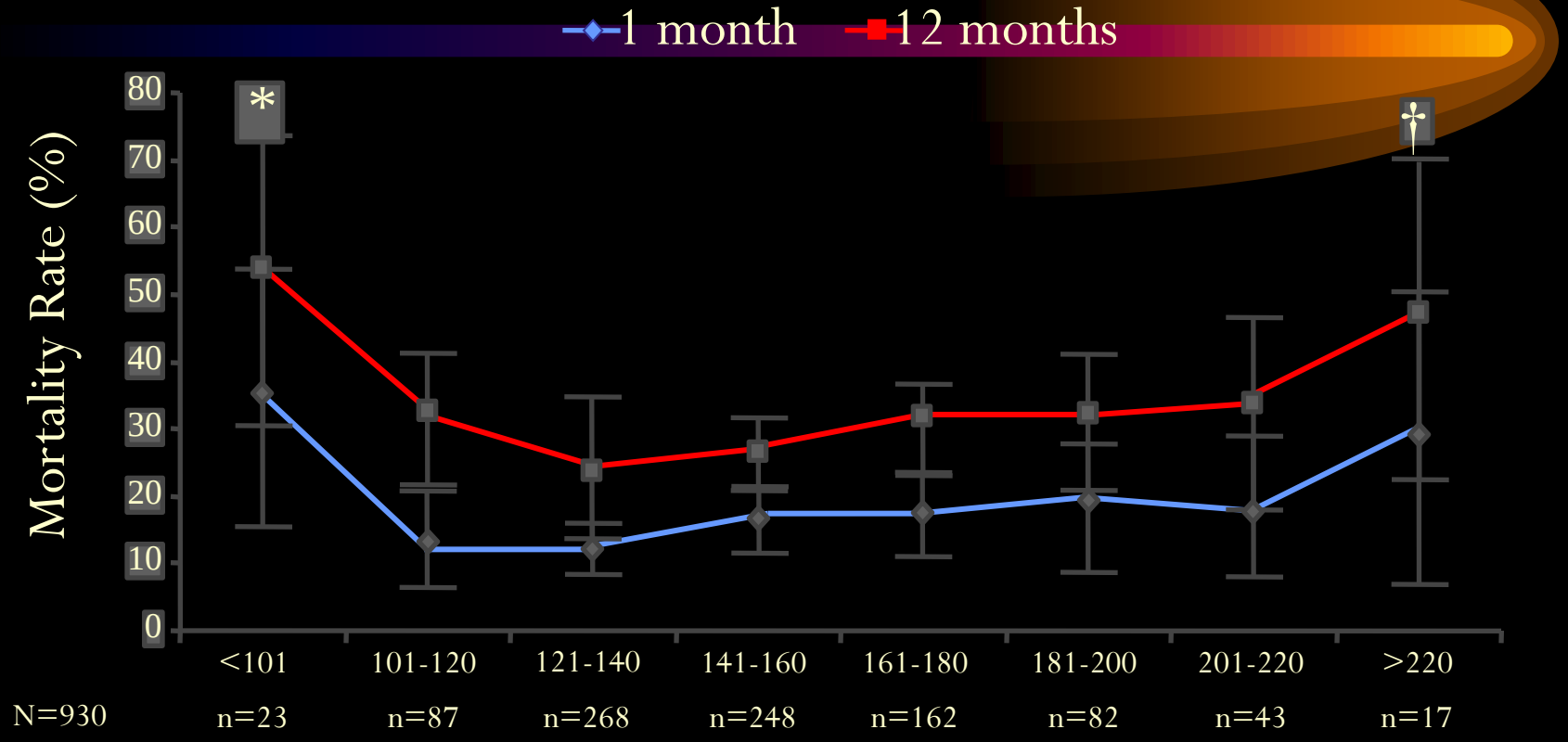
Nicardipine

- Selective arteriolar vasodilator[1,2]
- Calcium ion channel inhibitor[2]
- Onset of action: 5-10 minutes[3]
- Duration: 15-30 minutes; may exceed 4 hours[3]
- Adverse effects: tachycardia, headache, flushing, and local phlebitis[3]
  - No significant effect on ICP[4]
- Special indications/contraindications
  - Appropriate in most hypertensive emergencies except acute heart failure[1-3]

1. Rose JC, et al. *Neurocrit Care.* 2004;1:287-299. 2. Cardene I.V. (nicardipine hydrochloride). Prescribing information. Fremont, Calif: PDL BioPharma Inc; 2006. 3.The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Dept of HHS; NIH publication No. 04-5230; 2004:55. 4. Nishiyama T, et al. *Can J Anesth.* 2000;47:1196-1201. 5. Neutel JM, et al. *Am J Hypertens.* 1994;7:623-628.

Acute Ischemic Stroke

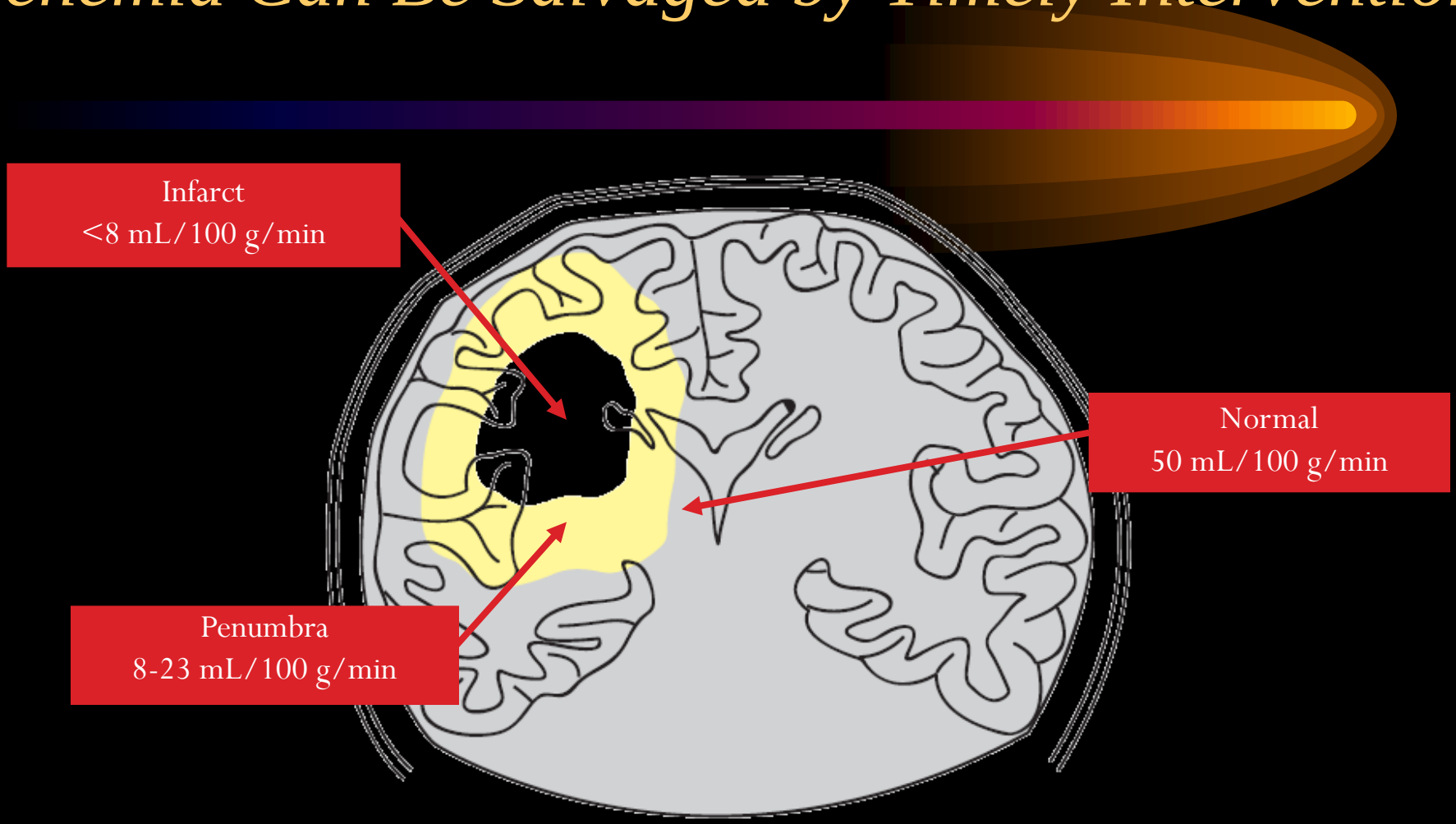
High or Low Admission SBP in IS Patients Correlates With Increased Early and Late Mortality



SBP = systolic blood pressure; IS = ischemic stroke.
*P<0.001 vs SBP 121-140 mm Hg on admission.
†P<0.05 vs SBP 121-140 mm Hg on admission.

Adapted from Vemmos KN, et al. *J Intern Med*. 2004;255:257-265.

Ischemic Penumbra: Hypoperfused Area of Focal Ischemia Can Be Salvaged by Timely Intervention



Ahmed SH, et al. In: Fisher M, ed. *Stroke Therapy*. 2nd ed. Woburn, Mass: Butterworth-Heinemann; 2001:25-57.
Ullman JS. In: Andrews BT, ed. *Intensive Care in Neurosurgery*. New York, NY: Thieme; 2003:29-46.

Treatment of Hypertension in Acute Ischemic Stroke: Concerns

- Without treatment
  - Formation of brain edema
  - Hemorrhagic transformation
  - Further vascular damage
- Overly aggressive treatment
  - Secondary reduction in perfusion to ischemic area

Adams HP, et al. *Stroke*. 2005;36:916-923.

AHA/ASA 2007 Treatment Guidelines for Arterial Hypertension: Ischemic Stroke Not Eligible for Thrombolytic Therapy

BP Level (mm Hg)	**Treatment**
SBP **≤220** *or* DBP **≤120**	Emergency administration of antihypertensive agents to be withheld
SBP **>230** *or* DBP **121-140**	**Nicardipine** or **labetalol** to **15% -25%** ↓ in BP within the first day
DBP **>140**	**Nitroprusside** to **15% -25%** ↓ in BP within the first day

ASA = American Stroke Association; IS = ischemic stroke; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Adapted from Adams HP, et al. *Stroke*. 2007;38:1655-1711.

AHA/ASA 2007 Treatment Guidelines for Arterial Hypertension: Ischemic Stroke Eligible for Thrombolytic Therapy

BP Level (mm Hg)	Treatment
Pretreatment SBP >**185** or DBP >**110**	**Labetalol** (may repeat once) or **nicardipine** If BP not reduced and maintained, do **not** administer rtPA
During and after rt-PA	
SBP **180-230** OR DBP **105-120**	**Labetalol**
SBP >**230** OR DBP **121-140**	**Nicardipine** or **labetalol** If BP not controlled, consider nitroprusside
DBP >**140**	**Nitroprusside**

Adapted from Adams HP, et al. *Stroke*. 2005;36:916-923.

Haemorrhagic Stroke

- The relationship between BP, intracranial pressure, and volume of haemorrhage is complex and not yet fully understood.

- The rationale for lowering BP is to minimise further haemorrhage - for example, from a ruptured aneurysm or arteriovenous malformation.

- However, in primary intracerebral haemorrhage, when a specific vasculopathy is not apparent, the risk from a mildly elevated BP may be lower, so aggressive reduction of BP must be balanced against the possible risk of inducing cerebral ischaemia in other brain areas.

- In cases of intracranial haemorrhage, target mean arterial pressure **(MAP) is 130** mmHg, with a goal of maintaining a cerebral perfusion pressure **(CPP) above 70** mmHg. Avoid BP dropping to below 110 mmHg.

- The first-line treatment is labetalol.
- If patients do not have evidence of raised intracranial pressure, a second-line treatment choice is nitroprusside.
- Nicardipine is another second-line agent which can be used.
- Nicardipine is especially useful in the presence of cardiac disease due to coronary vasodilatory effects.

Aortic Dissection

- If aortic dissection is suspected in a hypertensive emergency, the BP should be lowered quite aggressively, typically with a target of reducing systolic BP to **between 100 and 120 mmHg within 20 minutes.**
- Medical therapy aims to both lower the BP and decrease the velocity of left ventricular contraction, so decreasing aortic shear stress and minimising the tendency for propagation of the dissection.
- First-line treatment choice is beta-blockers, either labetalol or esmolol, administered intravenously.
- Second-line treatment choice would be the combination of nitroprusside and beta-blockers.
- Nitroprusside must be administered with a beta-blocker, as nitroprusside-induced vasodilation would otherwise induce a compensatory tachycardia and worsen shear stress on the intimal flap.

Myocardial Infarction

- First-line treatment of hypertensive emergency complicated by myocardial ischaemia or infarction is the combination of esmolol (a selective beta-blocker) plus glyceryl trinitrate (a peripheral vasodilator, which affects venous vessels more than arterial).
- Esmolol acts to reduce heart rate and glyceryl trinitrate acts to decrease preload and cardiac output and increases coronary blood flow.
- Second-line treatment choice would be labetalol plus glyceryl trinitrate.
- The third-line treatment choice would be nitroprusside.

LVF/ Pulmonary edema

- First-line treatment is glyceryl trinitrate.
- Nitroprusside (a potent arterial and venous vasodilator that decreases afterload and preload) is the second-line treatment choice in this situation.
- If patient is not already on one, a loop diuretic should be started (e.g., furosemide).

Acute Renal Failure

- Fenoldopam is the first-line treatment
- This drug (a selective peripheral dopamine-1-receptor agonist with arterial vasodilator effects) is particularly useful in renal insufficiency because it acts to both decrease afterload and increase renal perfusion.
- Second-line treatment choice is nicardipine

Hyperadrenergic States

- Hyperadrenergic states include:
- Phaeochromocytoma
- Sympathomimetic drug use – e.g. cocaine, amphetamines,, phencyclidine
- Following abrupt discontinuation of a short-acting sympathetic blocker.
- If the hyperadrenergic state is due to sympathomimetic drug use, the first-line agents are benzodiazepines
- In all other clinical situations, the first-line treatment choice is phentolamine (which acts by blocking alpha-adrenoceptors).
- The second-line treatment choice is the combination of labetalol plus nitroprusside.
- Administration of a beta-blocker alone is contraindicated due to risk of unopposed alpha-adrenergic vasoconstriction and a further rise in BP.

Eclampsia

- The first-line treatment choices are hydralazine, labetalol, or nicardipine.
- ACE inhibitors or ARBs are avoided due to potential teratogenic effects, and nitroprusside is avoided due to its potential for fetal cyanide poisoning.
- A guide target in these patients is to maintain a systolic BP of 130 to 150 mmHg and a diastolic BP of 80 to 100 mmHg.
- However, that there are no trials supporting these suggested thresholds, and treatments should be tailored to individual patient circumstances.
- In addition to the first-line treatments mentioned, it has been proposed that magnesium may be useful as an adjunctive therapy.

Take Home Message

- Accelerated hypertension is among the most misunderstood and mismanaged of acute medical problems seen in clinical practice
- Delays in initiating therapy can cause severe complications in target end organs
- Overzealous therapy resulting in a too-rapid reduction in blood pressure is equally damaging
- Many clinicians fail to consider the pathophysiologic principles involved in managing hypertensive emergencies and choose drug accordingly.

Thank You