Pathophysiology of HTN

Dr Badri Paudel

Overview

- HTN affects 43 million adults in US
- 95% have "essential HTN" without identifiable and treatable cause
- " Secondary" HTN accounts for ~5-10% of other cases and represents potentially curable disease
- Often overlooked and underscreened
- Controversy over screening and treatment in some cases

- Pathophysiology:
  - Some degree of sympathetic dysfunction is responsible for essential HTN
  - Dysfunction of the sympathetic nervous system leads to chronic vasoconstriction
  - Renal juxtaglomerular apparatus secretes renin
  - Angiotensin II is the major stimulus for the secretion of aldosterone

Causes of Secondary HTN

- Common
  - Intrinsic Renal Disease
  - Renovascular Dz
  - Mineralocorticoid excess/ aldosteronism
  - ? Sleep Breathing d/o
- Uncommon
  - Pheochromocytoma
  - Glucocorticoid excess/ Cushing's dz
  - Coarctation of Aorta
  - Hyper/hypothyroidism

Screening

- Testing can be expensive and requires clinical suspicion and knowledge of limitations of different tests
- General principles:
  - New onset HTN if <30 or >50 years of age
  - HTN refractory to medical Rx (>3-4 meds)
  - Specific clinical/lab features typical for dz
    - i.e., hypokalemia, epigastric bruits, differential BP in arms, episodic HTN/flushing/palp, etc

The Pathophysiology of Hypertension

- Blood pressure is generated by cardiac contraction against the vascular resistance, according to Ohm's Law:

  V = IR

  MAP = CO x SVR

  MAP = DBP + (SBP - DBP)/3

  CO = cardiac output

  SVR = systemic vascular resistance

Cardiac Output

- Cardiac output can be broken down as:
  - CO = SV x HR
  - SV = stroke volume
  - HR = heart rate
- Stroke volume is affected by pre-load, after-load, and contractility
- The primary determinant of cardiac output in normal individuals is volume status (sodium content)
- An increase in CO is rarely the cause of hypertension

Systemic Vascular Resistance

- SVR is affected by humoral and local factors.
- Humoral factors
  - Balance of vasoconstrictors and vasodilators
  - Angiotensin II and norepinephrine are two of the more important
- Local factors
  - Some arterioles are able to auto-regulate flow to their capillary beds, constricting at times of high blood pressure and dilating at times of low blood pressure
  - This is common in the brain and the kidney, and mediated by EDRF (NO)

Essential Hypertension

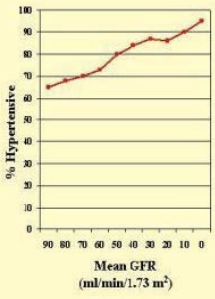
- No identifiable etiology
- Accounts for 90% of hypertension
- Onset typically in 40's to 50's
- Genetic pre-disposition
  - 70 - 80% of patients have a family history
  - Racial patterns

Secondary Hypertension

- Identifiable etiology
- Many of the factors that influence CO, SVR, and BP can be primarily disrupted by disease processes
  - Volume status - kidney disease and poor Na^+ handling
  - Angiotensin II – renal artery stenosis and perception by the kidney of hypo-perfusion despite conditions of hypervolemia
  - Aldosterone – primary hyperaldosteronism resulting in unregulated aldosterone production and sodium retention
  - Adrenergic tone – pheochromocytoma will result in excessive catecholamine production

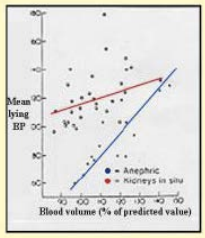
Kidney Failure

- With the loss of kidney function, virtually 100% of patients become hypertensive
- Chronic kidney disease is the most common form of secondary hypertension
- Hypertension can be cured with hemodialysis and ultrafiltration



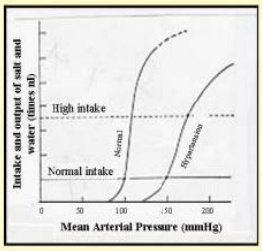
Impaired Sodium Excretion

- Blood volume correlates with SBP in patients with chronic kidney disease
- Blood pressure is very responsive to manipulations of volume status
- Seems to be mediated by abnormal vasoregulation and an increased SVR



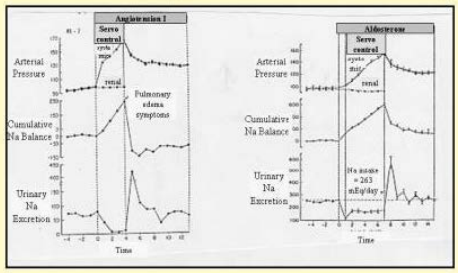
Impaired Pressure Natriuresis

- Chronic kidney disease results in a loss of the ability to alter sodium handling based on small changes in BP
- Impaired ability to handle sodium load



The Role of Pressure Natriuresis on Blood Pressure

The hypertensive response to AII and aldosterone is diminished when the increased pressure is transmitted to the kidney

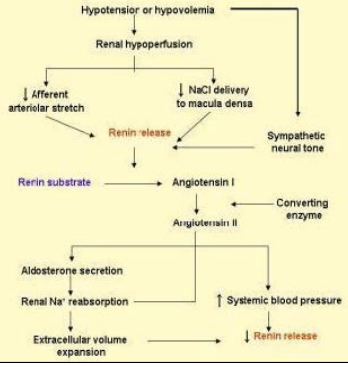


Contributions to Hypertension by the Kidney

The kidney plays an essential role in modulating systemic blood pressure by adjusting the sodium excretion rate. Sustained systemic hypertension is believed to necessitate a disturbance of this phenomenon, resulting in impaired sodium excretion. Modulation of sodium intake and sodium excretion (diuretics) effectively reduce blood pressure in the majority of patients.

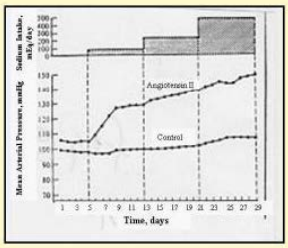
Renin – Angiotensin System

- Angiotensin II infusion causes hypertension
- Hypertensive patients drop BP much more significantly than euvolemic normotensive patients when angiotensin II is blocked



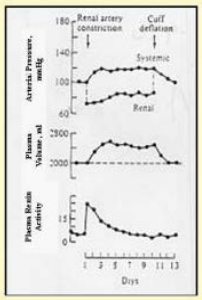
Effects of Angiotensin II

- Direct vasoconstriction and increased SVR
- Enhanced sodium reabsorption by the proximal tubule
- Stimulates aldosterone release with sodium reabsorption by the collecting tubule



Goldblatt Model I

- A clip is applied to **1 renal artery** in an animal with **2 functioning kidneys**
- Model of **unilateral renal artery stenosis**
- Hypertension due to unilateral RAS is associated with both an increased SVR and impaired natriuresis in the contra-lateral kidney

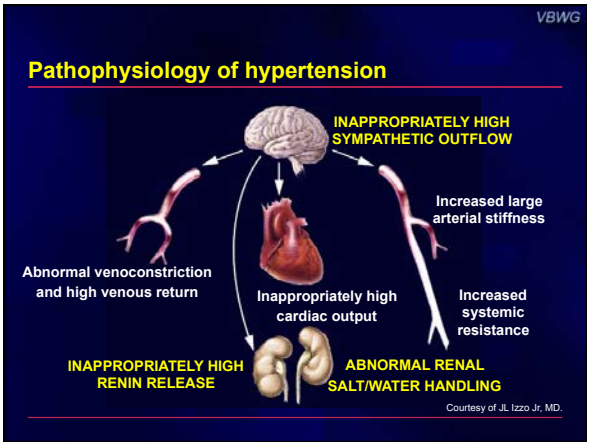


Goldblatt Model II

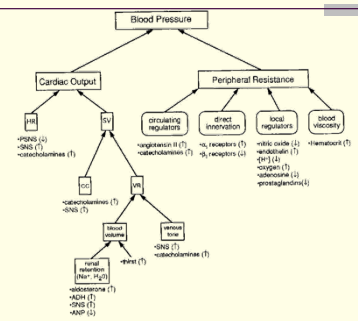
- A clip is applied to **1 renal artery** in an animal with **1 functioning kidney**
- Model of **bilateral renal artery stenosis**
- Total renal mass is hypo-perfused
  - Impaired clearance
  - Intolerance of ACE inhibitors
  - No off-setting pressure natriuresis

Sympathetic Nervous System

- Increased adrenergic tone leads to hypertension
- Blockade of the sympathetic nervous system reduces blood pressure
- Adrenergic tone increases
  - vascular tone
  - sodium retention
  - cardiac inotropy



Systemic HTN - Pathophysiology



Desmukh, et al. Pathophysiology of Heart Disease, Ch 13. 1997

Renal Parenchymal Disease

- Common cause of secondary HTN (2-5%)
- HTN is both cause and consequence of renal disease
- Multifactorial cause for HTN including disturbances in Na/water balance, depletion or antagonism of vasodepressors/ prostaglandins, pressor effects on TPR
- Renal disease from multiple etiology, treat underlying disease, dialysis/ transplant if necessary

Renovascular HTN

- Incidence 1-30%
- Etiology
  - Atherosclerosis 75-90%
  - Fibromuscular dysplasia 10-25%
  - Other
    - Aortic/renal dissection
    - Takayasu's arteritis
    - Thrombotic/cholesterol emboli
    - CVD
    - Post transplantation stenosis
    - Post radiation

Renovascular HTN

Safian & Textor. NEJM 344:6;p 432

Renovascular HTN - Pathophysiology

- Decrease in renal perfusion pressure activates RAAS, renin release converts angiotensinogen→ Ang I; ACE converts Ang I→ Ang II
- Ang II causes vasoconstriction (among other effects) which causes HTN and enhances adrenal release of aldosterone; leads to sodium and fluid retention
- Contralateral kidney (if unilateral RAS) responds with diuresis/ Na, H2O excretion which can return plasma volume to normal
- with sustained HTN, plasma renin activity decreases (limited usefulness for dx
- Bilateral RAS or solitary kidney RAS leads to rapid volume expansion and ultimate decline in renin secretion

Renovascular HTN - Clinical

- History
  - onset HTN age <30 or >55
  - Sudden onset uncontrolled HTN in previously well controlled pt
  - Accelerated/malignant HTN
  - Intermittent pulm edema with nl LV fxn
- PE/Lab
  - Epigastric bruit, particulary systolic/diastolic
  - Azotemia induced by ACEI
  - Unilateral small kidney

Renovascular HTN - diagnosis

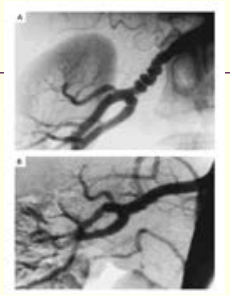
- Physical findings (bruit)
- Duplex U/S
- Captopril renography
- Magnetic Resonance Angiography
- Renal Angiography

Fibromuscular dysplasia

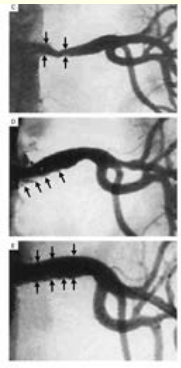
- 10-25% of all RAS
- Young female, age 15-40
- Medial disease 90%, often involves distal RA
- ~ 30% progressively worsen but total occlusion is rare
- Treatment – PTRA
  - Successful in 82-100% of patients
  - Restenosis in 5-11%
  - "Cure" of HTN in ~60%

Atherosclerotic RAS

- 75-90% of RAS
- Usually men, age>55, other atherosclerotic dz
- Progression of stenosis 51% @ 5years, 3-16% to occlusion, with renal atrophy noted in 21% of RAS lesions >60%
- ESRD in 11% (higher risk if >60%, baseline renal insufficiency, SBP>160)
- Treatment
  - PTRA success 60-80% with restenosis 10-47%
  - Stent success 94-100% with restenosis 11-23% (1yr)
  - "Cure" of RV HTN <30%



Fibromuscular Dysplasia, before and after PTRA



Atherosclerotic RAS before and after stent

Safian & Textor. NEJM 344:6;

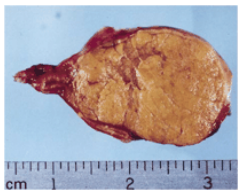
Primary Aldosteronism

- Prevalence .5- 2.0% (5-12% in referral centers)
- Etiology
  - Adrenal adenoma
  - Other: bilat adrenal hyperplasia, glucocorticoid suppressible hyperaldo, adrenal carcinoma
- Clinical:
  - May be asymptomatic; headache, muscle cramps, polyuria
  - Retinopathy, edema uncommon
  - Hypokalemia (K normal in 40%), metabolic alkalosis, high-nl Na

Primary Aldosteronism - Treatment

- Surgical removal of adrenal tumor, can be done laparoscopically
- Pretreatment for 3-4 wks with spironolactone minimizes postoperative hypoaldosteronism and restores K to normal levels, response of BP to spiro treatment is predictor of surgical outcome

Aldosteronoma



Obstructive Sleep Apnea

- Published reports estimate incidence of 30-80% of pt with essential HTN have OSA and 50% pt with OSA have HTN[1]
- Prospective studies show link between OSA (apneic-hyponeic index) and development of HTN independent of other risk fx[2]
- Clinical
  - Daytime somnolescence, am headaches, snoring or witnessed apneic episodes
- Dx – Sleep studies
- Rx – wt loss, CPAP, surgical (UPPP)

[1]Silverberg, et al.Curr Opinion Nephrol Hyperten 1998:7;353-361
[2] Peppard, et al. NEJM 2000;342:1378-1384

OSA – BP improvement with Rx

TABLE 1. MEAN (±SD) 24-HOUR BLOOD PRESSURE IN 17 HYPERTENSIVE AND 7 NORMOTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP APNEA WHO WERE TREATED WITH NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP).

BLOOD PRESSURE	BEFORE CPAP	AFTER 4–6 MO OF CPAP
	mm Hg	
Hypertensive patients		
Systolic	142±12	134±15*
Diastolic	91±9	84±7†
Normotensive patients		
Systolic	119±9	125±5
Diastolic	73±6	75±6

*P<0.05, by the Wilcoxon signed-rank test, for the comparison with the base-line value.
†P<0.005, by the Wilcoxon signed-rank test, for the comparison with the base-line value.

Pankow, et al. NEJM 343:966-967

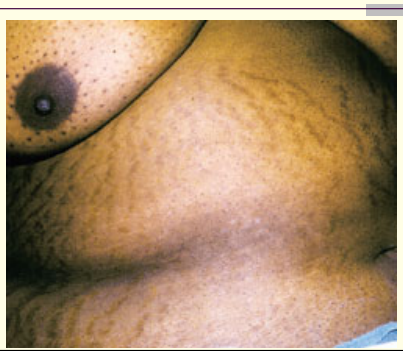
Pheochromocytoma

- Rare cause of HTN (.1-1.0%)
- Tumor containing chromaffin cells which secrete catecholamines
- Young-middle age with female predominance
- Clinical
  - Intermittent HTN, palpitations, sweating, anxiety "spells"
  - May be provoked by triggers such as tyramine-containing foods (beer,cheese,wine), pain, trauma, drugs (clonidine, TCA, opiates)

Cushing's syndrome/ hypercortisolism

- Rare cause of secondary HTN (.1-.6%)
- Etiology: pituitary microadenoma, iatrogenic (steroid use), ectopic ACTH, adrenal adenoma
- Clinical
  - Sudden weight gain,truncal obesity, moon facies, abdominal striae, DM/glucose intolerance, HTN,prox muscle weakness, skin atrophy, hirsutism/acne

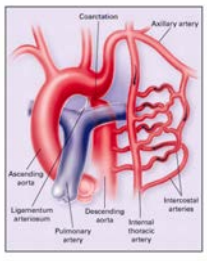
Cushings syndrome

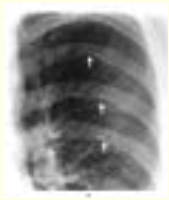


Coarctation of Aorta

- Congenital defect, male>female
- Clinical
  - Differential systolic BP arms vs legs (=DBP)
  - May have differential BP in arms if defect is prox to L subclavian art
  - Diminished/absent femoral art pulse
  - Often asymptomatic
  - Assoc with Turners, bicuspid AV
- If uncorrected 67% will develop LV failure by age 40 and 75% will die by age 50
- Surgical Rx, long term survival better if corrected early

Coarctation of Aorta





Brickner, et al. NEJM 2000;342:256-263

Hyperthyroidism

- 33% of thyrotoxic pt develop HTN
- Usually obvious signs of thyrotoxicosis
- Dx: TSH, Free T4/3, thyroid RAIU
- Rx: radioactive ablation, propanolol

Hypothyroidism

- 25% hypothyroid pt develop HTN
- Mechanism mediated by local control, as basal metabolism falls so does accumulation of local metabolites; relative vasoconstriction ensues

Summary

- Blood pressure is a result of cardiac output and systemic vascular resistance
- Essential hypertension is the most common cause of elevated blood pressure
- Disease processes that affect the determinants of blood pressure can result in secondary hypertension.
- These processes often affect sodium handling by the kidney, angiotensin II, aldosterone, and the sympathetic nervous system.