Objectives

• Identify the hemodynamic determinants of systemic hypertension

• Discuss the role of the kidney in systemic hypertension

• Describe the role of angiotensin II, aldosterone, and the sympathetic nervous system in the pathogenesis of hypertension

• Differentiate primary and secondary forms of hypertension

Blood Pressure

Blood Pressure is the product of Cardiac Output (CO) and Systemic Vascular resistance (SVR)

Blood Pressure is generated by cardiac contraction against Vascular resistance;

MAP = CO X SVR.

If one component increases the other must decrease proportionately to maintain normal BP or hypertension will result.
Blood pressure modulation by effects on cardiac output and peripheral resistance

Cardiac Output
- Stroke volume is affected by pre-load, after-load, and contractility
- The primary determinant of CO in normal individuals is volume status (sodium content)
- An increase in CO is rarely the cause of persistent hypertension

Systemic Vascular Resistance
- SVR is affected by humoral and local factors:
  - Humoral factors:
    - Balance of vasoconstrictors and vasodilators
    - Renin-Angiotensin System and norepinephrine are two of the more important factors.
  - Local factors:
    - Some arterioles are able to auto-regulate flow in their capillary beds, constricting at times of high BP and dilating at times of low BP.
    - This is common in the brain and the kidney, and mediated by Endothelium Derived Relaxing Factor (EDRF)
Sympathetic Nervous System

- Increased adrenergic tone leads to hypertension.
- Blockade of the sympathetic nervous system reduces BP
- Adrenergic tone increases
  - Vascular tone
  - Na⁺ retention
  - Cardiac inotropy
Hypothetical scheme for the pathogenesis of essential (primary) hypertension

Guyton Hypothesis and Renal Function Curves

- Fundamental mechanism of long term control of BP is the fluid volume feedback mechanism by Kidneys.
- Kidneys regulate arterial pressure by altering renal excretion of Na and water (Pressure Natriuresis) thereby controlling circulatory volume and cardiac output

Guyton AJM 52:584-594:1972
Guyton Hypertension: 10:1-6:1987

Renal Pressure Natriuresis

- Elevated BP raises sodium excretion usually accompanied by pressure diuresis (increased water excretion)
- In hypertension, sodium excretion (equal to sodium intake) is maintained at higher BP levels than that would normally result in natriuresis and diuresis
- Thus, in hypertensive subjects, pressure and diuresis are reset
Case History

- Mr. Brown is a 48 year old Caucasian man who works as a computer programmer. Recently he had physical examination at work and was told that his BP is elevated and advised to contact his physician. He has no problems or symptoms or complaints. He underwent a fully physical examination by his PCP. Systemic examination was normal but his BP was 145/92 (normal less than 140/90 in adults). His physician repeated his BP for three readings 2 minutes apart and they all were in that range. He tells his physician that no one in his family has hypertension. The patient is very active, goes to gym almost daily, and is normal weight for his height. He was advised to restrict his salt intake and return for follow-up in a week. His BP was now of 148/94. Rest of physical examination is normal. An extensive work done reveals no known cause of hypertension. His physician tells him he has Essential Hypertension and he will have to be on life-long therapy (lifestyle modification and medications) for hypertension. He is started on an ACEI and two weeks later his BP is now 130/85. Mr. Brown feels well and continues to work and engage in his normal activities.

Primary or Essential Hypertension

- No known etiology accounts for about 90-95% of hypertension.
- Occurs in cluster of families but it is not hereditary
- Polygenic, no single gene identify
- Monogenic hypertension is defined when a single gene is identified as the cause for hypertension

Derived Curves of Renal Handling of Salt and Water Intake in Normal People and in Patients with Essential Hypertension
Renal Pressure Natriuresis in Hypertension

- Renal pressure natriuresis is impaired and shifted in all forms of hypertension studied
- It may be due to either intra-renal or extra-renal factors yet to be fully described
- Intra-renal factors lead to reduced renal blood flow, decreased glomerular filtration rate or increased tubular reabsorption
- Extra-renal factors include increased sympathetic nervous system activity or increased anti-natriuretic hormones

Kidneys in Pathogenesis of Essential Hypertension

- No obvious renal defects identified in hypertensive patients so far but almost all experimental hypertension is caused by insult to kidneys altering either renal homodynamic or tubular reabsorption
- Renal pressure natriuresis mechanism is abnormal in all types of experimental and clinical hypertension

Hall, Hypertension 1990;15:547-559

Kidney Regulation of Normal Blood Pressure

- Maintenance of volume by regulating sodium excretion
- Pressure natriuresis an essential function of kidneys
- Resetting of pressure natriuresis at high level in essential hypertension
- Most monogenic hypertension due to increased sodium retention
Monogenic Hypertension

- Glucocorticoid remedial aldosteronism (GRM)
- Syndrome of apparent mineralocorticoid excess (AME)
- Mineralocorticoid receptor mutation (increases Na/Ca activity)
- Liddle Syndrome: gain of function ENac
- T594M mutation African-American subtype salt sensitive (increases ENac activity)

Pathways Affected in a Single Gene: Mendelian Hypertension and Hypotension Syndrome


Secondary Hypertension

- An explainable cause for hypertension is present
- May be superimposed on pre-existing essential hypertension
- Overall incidence is about 5-10% although in specific populations it may be >15-20%
Renovascular Hypertension

- Defined as resulting from stenosis of unilateral or bilateral renal artery stenosis
- Stenosis doesn’t necessarily mean hypertension
- Degree of stenosis is critical

Renal Artery Stenosis

- **Clinical presentations**
  - Severe and difficult to control hypertension
  - Kidney failure
  - Flash pulmonary edema

- **Two disease processes**
  - Atherosclerotic renal artery stenosis
  - Fibromuscular dysplasia
Renovascular Hypertension

- Unilateral renal artery stenosis with normal contralateral kidney
- Bilateral renal artery stenosis
- Renal artery stenosis in a solitary kidney

Goldblatt Model - I of Unilateral Renal Artery Stenosis with two kidneys

- A clip is applied to one renal artery in an animal with two functioning kidneys. That results renal artery stenosis on clipped artery.
- Results in hypo perfusion in clipped kidney, leads to increase secretion of renin–angiotensin.
- Increase BP results in pressure natriuresis in contralateral normal kidney, keeping near normal volume.
- Increase blood pressure maintained by increased TPR and some impaired pressure natriuresis.

Goldblatt Model II

- A clip is applied to one renal artery in an animal with one functioning kidney, a model of renal artery stenosis in a single kidney (such as renal artery stenosis in transplanted kidney).
- **Bilateral** renal artery stenosis:
  - Similar mechanism of hypertension.
  - Total renal mass is hypo-perfused
  - Impaired clearance
  - No off-setting pressure natriuresis (in contralateral kidney, thus absence or marked impairment of pressure natriuresis.)
Stenotic Kidney

- Suppressed Renin
- Pressure Natriuresis

Contralateral Kidney

Ischemia

Renin ↑

Angiotensin

Vasoconstriction.

Intrarenal Hemodynamics

Two Kidney-One Clip
(Unilateral Renal Artery Stenosis)

- BP ↑
- Blood Volume ↓
- Plasma Renin ↑
- Response to ACE-I (+)

One Kidney-One Clip
(Renal Artery Stenosis of a Solitary Kidney)

- BP ↑
- Blood Volume ↑
- Plasma Renin ↓
- Response to ACE-I (-)
Two Kidney-Two Clip
(Bilateral Renal Artery Stenosis)

- BP ↑
- Blood Volume ↑
- Plasma Renin →
- Response to ACE-I (-)

Renovascular Hypertension: Pathogenesis

- Unilateral renal artery stenosis with presence of normal contralateral kidney is vasoconstrictive maintained by increased RAS system
- Renal artery stenosis in solitary kidney or bilateral renal artery stenosis is volume dependent

Case 2

- Ms. Smith is a 61 year old woman with history of hypertension, hypothyroidism and asthma presents to renal clinic for evaluation of HTN. She reports that she was diagnosed with HTN about 5 years ago. Her BP has been difficult to control with systolic BP in 160s. Her regimen included Amlodipine 10mg daily and Metoprolol 50 mg twice daily.
- She had an episode of syncope and as part of work up had imaging of her brain. She also had CT angiogram of renal arteries and a subsequent procedure.
Renal Artery Stenosis

- **Therapy**
  - Medical – antihypertensives +/- ACE inhibitors
  - Interventional – renal artery angioplasty +/- stenting
  - Surgical – renal artery bypass

Aldosterone and Hypertension

- Aldosterone, a mineralocorticoid, is a sodium retainer
- Excess aldosterone leads to sodium and volume retention resulting in hypertension
- Primary aldosterone tumor is relatively rare but primary aldosteronism may result from adrenal hyperplasia and may be more common
Aldosterone

- Aldosterone results in Na retention and hypervolemia
- Excess potassium excretion leads of hypokalemia
- Volume expansion may be clinically absent due to “aldo-escape”
- Increased aldosterone leads to expanded ECV and hypertension.

Case 3

- 52 year old male was diagnosed with HTN for many years and was treated sporadically. His initial work up was normal with normal electrolytes except for low potassium of 3.3 mEq/L. His medications included Lisinopril and Amlodipine and Potassium chloride. His BP was better controlled with this regimen but low potassium persisted and Amiloride was added. He was lost to follow up. 3 years later, he had cardiac arrest in his office and was revived and his lab results showed serum potassium level of 2.5mEq/L. He had stopped taking Amiloride for an unspecified time.

Further work up

- Plasma renin activity: 0.17ng/ml/h
- Serum Aldosterone: 13ng/dl
- Serum Metanephrines: within normal range
- MRI abdomen: Left Adrenal adenoma 1 cm, Right adrenal normal.
- Adrenal vein sampling for aldosterone:
  - Right adrenal: 235 ng/dl
  - Left adrenal 27900 ng/dl
Chronic Kidney Disease and Hypertension

- As kidney function falls (↓ GFR), its ability to excrete sodium and water is impaired
- This leads to excess volume which causes and worsens hypertension

Impaired Sodium Excretion

- BP incidence increases with patients with chronic kidney disease
- BP is very responsive to manipulations of volume status
- Seems to be mediated by abnormal vasoregulation and increased SVR
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 controlled with diuretics and other hypotensive agents and in ESRD by hemodialysis and ultrafiltration.
Hypertensive Renal Injury

- Two patterns of Hypertension injury to Kidneys
  - Essential hypertension
    - Benign nephrosclerosis.
  - Malignant hypertension
    - Intimal thickening
    - Proliferative arteritis
    - Fibrinoid necrosis
    - Renal auto regulation.
**Essential Hypertension and Nephrosclerosis**

- Contracted kidneys in essential hypertension
- Progressive reduction in size
- Cortical atrophy and diffuse fibrosis
- Afferent arteriolar hyaline arteriosclerosis
- Subintimal hyaline homogenous eosinophilic deposits
- Ischemic atrophy

**Nephrosclerosis**

![Image of Nephrosclerosis](image1)

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Malignant Hypertension

- Marked elevation of BP
- Evidence of widespread acute arteriolar injury
- Fundoscopic finding of hypertensive neuroretinopathy

Nolan 2001
Autoregulation

- Autoregulation of glomerular filtration rate (GFR) and renal blood flow (RBF) is due to pre-glomerular vasoconstriction that impedes the transmission of elevated systemic arterial pressure to glomerulus and peritubular capillaries of the kidneys.
- Autoregulation protects kidneys from hypertensive injury but may be altered in chronic kidney disease and diabetic kidney disease.

Autoregulation of Renal Blood Flow & GFR

- Ensures that renal blood flow and GFR remain relatively constant even while systemic arterial pressures fluctuate.
- Depends primarily on two mechanisms:
  - Myogenic Response
  - Tubuloglomerular Feedback

![Autoregulatory range graph]

![Blood Flow and GFR graph]

FIG. 8a
Myogenic Response

- Response to increased afferent arteriolar pressure:
  - stimulates reflexive vasoconstriction by stimulating smooth muscle cell contraction
  - minimizes increase in P_{GC} that would otherwise occur in response to increased systemic arterial pressure
  - prevents damage to glomerular capillaries, which already function at hydrostatic pressures that are much greater than those in the systemic capillaries

- Response to decreased afferent arteriolar pressure:
  - stimulates reflexive vasodilation by stimulating vascular smooth muscle relaxation
  - increases blood flow and filtration pressure in the glomerulus, thereby helping maintain GFR

Renal autoregulation prevents transmission of systemic blood pressure to glomerular capillaries
Systemic hypertension would increase glomerular capillary pressure in absence of autoregulation

\[ \text{BP}^* \rightarrow \uparrow \rightarrow \text{A} \rightarrow \text{G} \rightarrow \text{E} \]

Dihydropyridine calcium antagonists abolish renal autoregulation and prevent normalization of glomerular capillary pressure

\[ \text{DCA} \rightarrow \text{BP}^* \rightarrow \uparrow \rightarrow \text{A} \rightarrow \text{G} \rightarrow \text{E} \]

Kidney Autoregulation: Therapeutic role

- Autoregulation of kidneys modulate blood flow and pressure transmission to glomerular tufts and protects them against injury.
- In CKD or diabetes, autoregulation is impaired making kidney more prone to hypertensive injury.
- Some antihypertensive drugs may abolish autoregulation and may worsen renal injury.
Treatment of Hypertension: Renal Considerations

- Lowering BP will minimize damage to kidneys and slow down progression of renal failure
- In presence of chronic kidney disease, sodium and water are retained and volume becomes an important factor
- Diuretics are necessary in most instances of hypertension with CKD
- Drugs which preserve renal autoregulation help preserve renal functions

Summary

1. Kidneys play a central role in long term regulation of blood pressure and hypertension

2. There is shifting of pressure natriuresis curve to right in essential hypertension or reset at higher BP level

Summary

3. Unilateral renal artery stenosis with a normal contralateral kidney is renin dependent and blocking the renin-angiotensin system is an effective treatment

4. In bilateral renal artery stenosis and in stenotic solitary kidney, the hypertension is volume related
Summary

5. Interaction of volume and vasoconstriction is responsible for the vast majority of essential hypertension

6. Kidneys are prone to hypertensive injury and keeping blood pressure under control prevents development of renal failure

QUESTIONS?

Blood Pressure = Cardiac Output x Peripheral Resistance
Hypertension = Increased CO x Increased PR

- Stroke Volume
- Contractibility
- Functional Constriction
- Na Balance
- Catecholamines
- Renin
- Angiotensin
- Catecholamines
Renin Angiotensin System in Hypertension

- Renin angiotensin system has major effect in pathogenesis and maintenance of hypertension via angiotensin II
- Direct vasoconstriction and increased SVR
- Enhanced Na reabsorption by the proximal tubule
- Stimulates aldosterone release which increases Na reabsorption by the collecting tubule