# Objectives

- 1. Understand the hemodynamic determinants of systemic hypertension.
- 2. Recognize primary and secondary forms of hypertension.
- 3. Understand the role of the kidney in systemic hypertension: innocent bystander or instigator.
- 4. Recognize the role of angiotensin II, aldosterone, and the sympathetic nervous system in the pathogenesis of hypertension.

# I. Hemodynamic Determinants of Systemic Hypertension

A. Blood pressure – Pressure is generated when the heart contracts against the resistance of the blood vessels. Ohm's Law can be applied as follows:

V = I x R MAP = CO x SVR MAP = mean arterial blood pressure, estimated by DBP + (SBP - DBP)/3 CO = cardiac output SVR = systemic vascular resistance

Cardiac output can be broken down as:

CO = SV x HR SV = stroke volume (dependent on pre-load, contractility, after-load) HR = heart rate

- B. Systemic hypertension necessitates an increase in CO and/or SVR.
  - 1. Typically, hypertension results from an **increase in SVR with normal CO**. However,
    - a. In young patients with borderline hypertension, or intermittently hypertensive patients, increased CO may be the only hemodynamic disturbance (possibly due to an increased sympathetic tone). With time, CO "normalizes" and SVR increases to sustain the hypertension.
    - b. Even in disorders that are clearly associated with volume overload, e.g. kidney failure, the increase in cardiac output is transient followed by an increase in SVR. The mechanism of increased SVR in this setting is unclear.

- C. Modulators of CO
  - 1. ECF (total body sodium content, **NOT** plasma sodium concentration) this is regulated by sodium handling by the kidney
  - 2. Contractility/Heart Rate sympathetic tone, other inotropic effectors
- D. Modulators of SVR balance of vasoconstrictors and vasodilators
  - 1. Humoral factors
    - a. Sensors baroreceptors, JG apparatus, atrium
    - b. Mediators blood pressure, distal tubule chloride delivery, atrial stretch
    - c. Effectors:
      - i. Vasoconstrictors angiotensin II, norepinephrine, thromboxane, endothelin, others
      - ii. Vasodilators prostaglandins, bradykinin, atrial natriuretic peptide
      - iii. Other effects altered Na<sup>+</sup> excretion by the kidney and manipulation of ECF
  - 2. Local factors The vessel wall, in particular the endothelial monolayer, is able to transduce both mechanical and chemical signals into appropriate changes in vascular smooth muscle tone under normal circumstances. This transduction is mediated by direct electrical connections between the endothelium and the vascular smooth muscle, as well as the ability of the endothelial cell to elicit soluble paracrine factors.
    - a. Mediators endothelial cell and vascular smooth muscle cell
    - b. Signals blood pressure, shear stress (related to blood flow/viscosity, vessel diameter), humoral factors
    - c. Effectors
      - i. Vasoconstrictors myogenic response, prostaglandins, leukotrienes, endothelin, endothelium-derived constricting factor (EDCF), angiotensin, endothelial cationic channels, oubain-like factor
      - ii. Vasodilators endothelium-derived relaxing factor (EDRF, a.k.a. nitric oxide), prostaglandins, endothelial ionic channels

d. Local mechanisms allow for autoregulation of blood flow and capillary pressure to various organs (brain and kidney most prominently). They also allow for modulation of hemodynamics in an individual vascular bed with lesser changes in systemic hemodynamics.

## **II. Primary and Secondary Hypertension**

- A. Primary or "Essential" Hypertension
  - 1. Etiology unknown
  - 2. Accounts for approximately 90% of hypertension
  - 3. Onset typically in the fifth or sixth decade of life
  - 4. Strong family history 70-80% positive family history
    - a. If hypertension in both parents, risk of hypertension in off-spring is increased by 250%
    - b. BP correlations are stronger among parent and child than between spouses, suggesting that environmental factors are less important than genetic ones
    - c. Certain races (e.g. African Americans) are at much higher risk of hypertension
- B. Secondary Hypertension
  - 1. Identifiable underlying cause:
    - a. kidney disease
    - b. renal artery stenosis
    - c. hyperaldosteronism
    - d. pheochromocytoma
  - 2. Represents approximately 10% of all hypertension
  - 3. Has specific therapy, and is potentially curable
  - 4. Often distinguishable from essential hypertension on clinical grounds

- C. Approach to understanding potential mechanisms of hypertension
  - 1. Identify demographics unusual to see new-onset essential hypertension in children or the elderly, family history of essential hypertension, race
  - 2. Identify co-morbid conditions i.e. RAS is an extension of peripheral vascular disease

#### III. Role of the kidney in systemic hypertension

- A. Evidence
  - 1. With progressive loss of kidney function, virtually 100% of patients become hypertensive
  - 2. Chronic kidney disease is the most common form of secondary hypertension
  - 3. Hypertension frequently improved or "cured" with hemodialysis



- B. Hypothesis I Kidney failure leads to impaired sodium excretion, resulting in expansion of the ECF, volume overload, and subsequent systemic hypertension.
  - 1. Evidence supporting Hypothesis I
    - a. Blood volume correlates with systemic blood pressure in patients with advanced kidney disease.
    - b. Systemic hypertension due to kidney disease frequently responds to maneuvers that reduce ECF volume:
      - i. sodium restriction
      - ii. diuretics
      - iii. ultrafiltration (part of dialysis)
  - 2. Mechanism of hypertension
    - a. Despite clear-cut volume expansion, cardiac output is near normal. Hypertension is primarily due to **an increase in SVR.**
    - b. Suggests abnormal vasoregulation, possibly related to SNS and RAAS.

C. Hypothesis II - Impaired kidney sodium excretion is necessary to sustain all forms of hypertension.



Pressure natriuresis in normals and hypertensives

- 1. Persistent hypertension necessitates abnormal pressure natriuresis phenomena
  - a. Small changes in systemic BP should lead to marked changes in sodium excretion rates by the kidney
  - b. In normals, increased sodium intake leads to ECF expansion, increased CO and BP, increased kidney Na<sup>+</sup> excretion, and normalization of hemodynamics.
  - c. Hypertension must be associated with resetting of this mechanism at a higher blood pressure. Although both normotensive and hypertensive patients are in a steady state (intake = output), the hypertensive patients achieve this balance at a higher blood pressure.
  - d. With increased dietary Na<sup>+</sup>, the hypertensive patients increase BP to a greater extent (note less steep slope)

- 2. Why is the pressure natriuresis curve reset? Possible explanations include:
  - a. augmented sodium reabsorption distal to the site of pressure natriuresis
  - b. fewer functioning nephrons
  - c. kidney vasoconstriction (an early finding in hypertension) leading to less "transmission" of BP to site of pressure natriuresis
  - d. increase in proximal sodium reabsorption
- D. Importance of pressure natriuresis phenomena in determining sodium handling by the kidney and systemic blood pressure in two models of secondary hypertension.



1. Key points:

Figure 3

- a. Holding kidney perfusion pressure constant leads to sodium retention and severe progressive hypertension in the presence of either AII or aldosterone
- b. Hypertension is substantially reduced by exposing the kidney to the higher perfusion pressure, temporally related to natriuresis

- E. Evidence of a primary role of impaired kidney sodium excretion in the pathogenesis of a genetic model of systemic hypertension.
  - 1. Cross transplantation of kidneys from hypertension-prone strains of rats (Dahl saltsensitive rat and SHR) to their normotensive counterparts leads to sodium retention and systemic hypertension.
  - 2. Transplantation of kidneys from hypertension-resistant to hypertension-prone rats confers protection.

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

#### IV. Role of the Renin-Angiotensin System in Systemic Hypertension

- A. Evidence
  - 1. AII infusion/overproduction causes hypertension
  - 2. ACE inhibitors have little effect on BP in euvolemic normotensive patients
  - 3. ACEi and AII receptor antagonists decrease BP in 60-70% of hypertensive patients.
- B. Mechanism of Hypertensive Effects
  - 1. Angiotensin II directly induces vascular smooth muscle contraction.
  - 2. Angiotensin enhances Na<sup>+</sup> reabsorption



C. Goldblatt Model - Hypertension in the **one clip/two kidney** animal (model for unilateral renal artery stenosis)

- 1. Mechanism of Hypertension
  - a. Severe reduction in JG apparatus pressure (requires >70-80% stenosis)
  - b. Kidney hypo-perfusion leads to renin production, which leads to increased AII and aldosterone
  - c. AII causes direct vasoconstriction
  - d. All and aldosterone increase sodium reabsorption





- 2. Does the unaffected contra-lateral kidney reduce BP by inducing a profound pressure natriuresis? Why isn't the blood pressure normalized?
  - a. AII-mediated constriction in the contra-lateral kidney decreases the amount of pressure transmitted to the proximal tubule and loop on Henle (region believed responsible for pressure natriuresis)
  - b. Direct effects of AII on  $\mathrm{Na}^{\mathrm{+}}$  transport in the proximal tubule of the contra-lateral kidney
  - c. Evidence that this impaired pressure natriuresis is AII-mediated: ACEi increase Na<sup>+</sup> excretion dramatically in the **non**-stenotic kidney despite reductions in BP

d. Release of unilateral stenosis in rats results in a profound natriuresis.

# Conclusion: Hypertension due to unilateral RAS is associated with both an increased SVR and impaired natriuresis in the contra-lateral kidney

- D. Hypertension in the **one clip/one kidney** animal (model for bilateral renal artery stenosis)
  - 1. Total kidney mass is hypo-perfused (no normal kidney) and kidney function/clearance is jeopardized
  - 2. No off-setting effects on sodium balance by pressure natriuresis in a normal kidney
- E. Renal Artery Stenosis in Humans
  - 1. Clinical characteristics
    - a. Usually severe hypertension
      - i. requires multiple antihypertensive agents
      - ii. can induce malignant hypertension (rapid end-organ damage)

iii. more likely to be refractory to medical management

- b. Clinical clues
  - i. demographics old, white, male, smokers in wheelchairs after amputations
  - ii. high blood pressure with low K (due to increase aldo)
  - iii. bruits
- 2. Diagnosis Peripheral plasma renin activity is rarely diagnostic. Usually requires radiographic visualization of kidney arteries and venous sampling of renin (disparity of stenotic kidney vein renin concentration compared to infra-kidney IVC renin concentration the distal most blood from the kidneys).
- 3. Pathology
  - a. Atherosclerotic Renal Artery Disease
    - i. 90% of renal artery stenosis
    - ii. extension of peripheral vascular disease
    - iii. typically affects older vasculopaths

- b. Fibromuscular Dysplasia
  - i. disease affecting the media of the kidney artery produces a beaded, aneurysmal appearance on imaging
  - ii. typically affects younger women third and fourth decade of life
- 4. Therapy
  - a. Medical Anti-hypertensive therapy and blood pressure control is often successful in preventing end-organ damage from hypertension. ACEi risks kidney function in bilateral renal artery stenosis where kidney perfusion and GFR are highly dependent upon angiotensin II.
  - b. Interventional renal artery angioplasty and stenting
  - c. Surgical renal artery by-pass

## V. Role of Aldosterone in Systemic Hypertension

- A. Evidence
  - 1. Patients with adrenal hyperplasia and/or adenomas (rarely malignant tumors) that produce excess aldosterone usually develop hypertension
  - 2. Infusion of mineralocorticoids in animals induces hypertension
- B. Pathogenesis of hypertension in primary hyperaldosteronism
  - 1. Aldosterone stimulates Na<sup>+</sup> retention and hypervolemia
- C. Clinical characteristics
  - 1. Hypertension can range from mild to extreme (malignant)
  - 2. No "obvious volume" expansion (i.e. no edema) due to "aldo-escape"
  - 3. Often spontaneous hypokalemia, particularly evident with high salt diet and diuretic therapy
  - 4. Low PRA, and "normal" to high 24 hour urine aldosterone excretion inappropriate!!!
  - 5. Usually easily treated with K<sup>+</sup> sparing diuretics (spironolactone, amiloride)
  - 6. Surgically curable

## **Pathophysiology of Hypertension**

- D. Role of aldosterone in essential hypertension
  - 1. Note that the distribution of aldo levels in essential hypertension, i.e. approximately 70% are "normal" or above normal. Despite this range, patients with essential hypertension have normal potassium levels.
  - 2. Patients with primary hyperaldosteronism have very high levels with only small overlap with essential hypertension.
  - 3. Must follow-up with imaging of adrenal (CT)



Figure 6

## VI. Role of the Sympathetic Nervous System (SNS) in Systemic Hypertension

A. Evidence

- 1. Increased SNS tone leads to hypertension (pheochromocytoma, emotional stress)
- 2. Norepinephrine (NE) levels are normal or low in most patients. What is normal in the hypertensive patient? There is a possible resetting of baroreflexes such that increased SNS tone contributes to maintenance of hypertension
- 3. Sympathetic blockers lower blood pressure in the majority of patients.
- B. Mechanism
  - 1. The SNS is a major player in the regulation of normal circulatory hemodynamics
    - a. Norepinephrine, like AII, directly stimulates vascular smooth muscle contraction and thus SVR through receptor mediated binding
    - b. Norepinephrine, like AII, induces kidney sodium retention
    - c. Norepinephrine stimulates renin release
  - 2. Effects might be modulated by factors other than NE concentration and sympathetic tone, such as receptor density and affinity

#### C. Pheochromocytoma

- 1. Clinical characteristics
  - Tumor that secretes either NE or NE/Epi (Adrenal gland, sympathetic chain)
  - b. **RARE** more common in patients with severe hypertension
  - c. Associated with other signs of catecholamine excess including sweating and palpitations



- d. Difficult to diagnose
  - i. careful measurements of catecholamines in the urine and plasma
  - ii. extensive radiographic evaluation
- e. Tumors generally benign, and hypertension curable with resection.
- D. Role of SNS in Essential Hypertension similar to AII and aldosteronism, patients with essential hypertension have a wide range of activation of SNS.

#### VII. Conclusion

Systemic hypertension is primarily due to an increase in systemic vascular resistance and not an increase in cardiac output. Hypertension is associated with impaired kidney sodium excretion, reset baroreflexes, and reset local autoregulation responses. Alterations in the renin-angiotensinaldosterone system and sympathetic nervous system are likely to play a role in the generation and maintenance of hypertension, due to their direct effects on kidney vascular tone and sodium excretion.