I. Hemodynamic Determinants of Systemic Hypertension

Blood pressure (BP) is generated by the heart contracting against the resistance of blood vessels. BP is tightly controlled to provide adequate organ perfusion. Normal BP levels are established by epidemiology and outcome studies.

BP is defined as: CO x TPR where CO is cardiac output and TPR is total peripheral resistance (or SVR, systemic vascular resistance).

CO is dependent on stroke volume (SV) and heart rate (HR), thus

\[ BP = [(SV \times HR) \times TPR] \]

CO depends on blood volume which varies directly with the total sodium (Na) content because Na is the predominant extracellular solute that retains water within extracellular space. SV is dependent on preload, contractility, and afterload.

\[ \text{Hypertension} = \text{Increased Cardiac Output} \times \text{Increased Peripheral Resistance} \]

- Stroke Volume
- Contractibility
- Functional Constriction
- Na Balance
- Catecholamines
- Renin Angiotensin Catecholamines

The primary function of the kidneys is to regulate Na and water excretion, and consequently they play a dominant role in the long term regulations of BP.

Mean arterial pressure (MAP) = Diastolic blood pressure (DBP) + 1/3 (Systolic blood pressure (SBP) – DBP).

Systemic hypertension necessitates an increase in CO and/or TPR (SVR).
Modulators of CO:

1. Extracellular fluid (ECF) as body sodium content not plasma sodium concentration. This is regulated by sodium handling of the kidneys.
2. Contractility as HR (sympathetic tone and other inotropic effectors).

Modulators of SVP:

1. Humoral factors:
   a. Sensors: baroreceptors, JG apparatus atrium
   b. Mediators: BP, distal tubule chloride delivery, atrial stretch
   c. Effectors:
      i. Vasoconstrictors: angiotensin II, norepinephrine, thromboxane, endothelin, and others
      ii. Vasodilators: prostaglandins, bradykinin atrial naturetic peptide
      iii. Others: effects-altered Na excretion by kidney and manipulation ECV

2. Local factors:
   a. The vessel wall, endothelium monolayer, vascular smooth muscle cell
   b. Signals-blood pressure, shear stress, generated by blood flow (viscosity), 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 relating factor (EDRF, nitric oxide)

Local mechanism allows for auto regulation of blood flow and capillary pressure to various organs (brain and kidney most prominently)

II. Renal Mechanisms of Hypertension

Two renal mechanisms are used to achieve BP regulation:
1. **Pressure Natriuresis:** This first mechanism regulates the extracellular fluid volume, by coupling increasing or decreasing urinary excretion of Na and water and related changes in blood volume and cardiac output to changes in renal perfusion pressure.

2. **Renin-Angiotensin-Aldosterone:** The second mechanism employs the renin angiotensin aldosterone system which directly controls peripheral resistance and renal reabsorption Na and water. Thus kidneys regulate long term BP both at cardiac output and peripheral resistance components. Total peripheral resistance (TPR) equates vasoconstriction. The renin-angiotensin system depends to a large part on the kidneys. Renin is secreted by the juxta-glomerular, acts on angiotensinogen converting it to angiotensin I which is then acted on by converting enzyme resulting in angiotensin II.

   In essence kidneys may regulate blood pressure both at volume (Na) and at vasoconstriction level (renin-angiotensin)

**Concepts of total body regulation:**

Tissues normally adjust vascular resistance to maintain constant flow (perfusion)

Should resistance remain the same, cardiac output will increase tissue perfusion because of increased blood pressure.

Thus it is postulated that hypertension causes auto regulatory increases in vascular resistance at the individual tissue level leading to the overall increased TPR to prevent over-perfusion of tissues.

**Hemodynamics of established hypertension.**

Initially CO may be increased in hypertension. However, once established the major abnormality is increased TPR. This evolution of hemodynamic, i.e., from increased CO, to increased TPR remains unexplained, but it is probably due to total body autoregulation.
Pressure Natriuresis

Pressure natriuresis is the increase in urinary excretion of Na and water in response to increase in arterial BP. This compensatory response is the way kidneys regulate BP within normal range by adjusting blood volume. The kidney regulates the excretion of water and electrolytes through a tightly controlled balance of glomerular filtration, tubular reabsorption and secretion. Impaired pressure natriuresis may lead to hypertension. In almost all experimental models of hypertension, pressure natriuresis is impaired. In essential or primary hypertension, a high level of blood pressure is required to affect diuresis.

Guyton introduced the concept of “renal functional curves”, a relationship between blood pressure and sodium excretion. Each individual has a set point beyond which blood pressure rises. The relationship between pressure and diuresis is called the renal functional curve. In hypertension this curve shifts towards the right in which high blood pressure is required to affect diuresis and maintain volume. The kidney functions as servo-controller of arterial pressure and exhibits an infinite negative feedback gain for long term regulation of arterial pressure by adjusting blood volume.

Key point: Impaired pressure natriuresis is fundamental aspect of human hypertension and all experimental models of hypertension.

III. Role of Sympathetic Nervous System (SNS) in Systemic Hypertension

SNS plays an important role in regulation of normal circulatory hemodynamics. Norepinephrine directly stimulates vascular smooth muscle contraction and thus affects SVR/TPR.

SNS, like angiotensin II, leads to Na retention.

Nor-epinephrine stimulates renin secretion.

Increased SNS tone leads to hypertension (pheochromoctyoma, emotional stress). Although nor-epinephrine is normal or low in most patients with essential hypertension, there may be some resetting of baroreceptor reflexes that increase the SNS tone and maintain high BP.
Role of Renin – Angiotensin in Systemic Hypertension

**Evidence:** Angiotensin II infusion /over production causes hypertension.

Drugs which block the action of angiotensin, such as angiotensin converting inhibitors or receptor blockers or direct renin inhibitors have little or no effect in euvoilemic normotensive patients whereas in hypertensive patients they are very effective in lowering BP in about 70% of patients regardless of the renin levels.

The role of renin-angiotensin in causing hypertension is discussed in section on reno-vascular hypertension.

Role of Aldosterone in Systemic Hypertension

Aldosterone stimulates Na retention by kidneys thus effecting volume. Infusion of mineralocorticoid such as aldosterone produces hypertension in laboratory animals,

Adrenal hyperplasia or adrenal adenomas produce excessive aldosterone and usually develop hypertension or primary hyperaldosteronism and aldosterone blockers are effective in reducing BP. Aldosterone leads to volume expansion, low renin levels, and may present as hypokalemia or low serum potassium.

If adenoma is found to be the cause for excess aldosterone production, it can be surgically removed (hypertension cured).

IV. Primary versus Secondary Hypertension

**Primary Hypertension:** In the vast majority of persons (>90%), the hypertension is primary or essential hypertension. It is generally accepted that primary hypertension is a polygenic disorder, i.e., multiple genes are likely to contribute to hypertension.

Hypertension can be due to a primary increase in volume (increased cardiac output) or due to increase in peripheral resistance (vasoconstriction) or both. It is not yet possible to reach a consensus as to whether the volume or vasoconstriction mechanism is primarily responsible for the hypertension. For
example, when hypertension has been initiated by increased volume there is concurrent rise in total peripheral resistance (TPR) over the time volume normalizes. However, elevated TPR sustains the hypertension. Almost all patients with established hypertension exhibit the same hemodynamic profile of a normal cardiac output and increased peripheral resistance.

A. Primary or essential hypertension is where no etiology has been identified so far and is 90% of the prevalence of hypertension.

B. Hypertension may be due to a primary increase in volume (cardiac output) or due to increase in total peripheral resistance (vasoconstriction). It is not possible to delineate these in clinical practice and it appears that in the majority of the patients both may play a role.

C. Primary hypertension occurs in cluster of families; present in family history but is not hereditary.

D. No single gene is identified except in a minuscule subset of hypertension (monogenic hypertension)

E. Monogenic Hypertension is where a single gene mutation has been identified resulting in hypertension. The incidence of such hypertension is rare. Almost all the genetic mutation involves increased Na reabsorption resulting in increased BP pressure.

F. Essential hypertension is believed to be polygenic where several genes may be involved.
Secondary Hypertension: In small percentage of hypertensive’s (less than 10%), there may be a definite pathogenic mechanism leading to hypertension. That is known as secondary hypertension. It may be possible to identify the main pathogenic mechanisms in secondary hypertension and label them as primarily volume mediated or vasoconstrictor. (See listed in Table 1). Even then, the mechanisms may overlap.

Table 1. Some Secondary Causes of Hypertension

<table>
<thead>
<tr>
<th></th>
<th>PRIMARILY VOLUME MEDIATED</th>
<th>PRIMARILY VASOCONSTRICTOR MEDIATED</th>
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<tbody>
<tr>
<td>Non-renal causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Primary hyperaldosteronism</td>
<td>1. Pheochromocytoma</td>
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<tr>
<td>2.</td>
<td>Cushing’s syndrome</td>
<td>2. Unilateral renal artery stenosis</td>
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<tr>
<td>3.</td>
<td>Mineralocorticoid producing tumors</td>
<td>3. Hypercalcemia</td>
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<tr>
<td>Renal causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Acute glomerulonephritis</td>
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</tbody>
</table>

Pheochromocytoma: A tumor of adrenal medulla which produces excessive amounts of epinephrine and nonepinephrine. This increased level of catecholamine produces severe hypertension due to intense vasoconstriction.

Primary Aldosteronism: A tumor or hyperplasia of adrenal cortex leads to increased production of aldosterone. Aldosterone leads to sodium retention and expanded volume leading to severe hypertension. This is pure volume expansion. The plasma levels of aldosterone are increased and that of plasma renin are suppressed.

Renovascular Hypertension

A. This is the most common cause of secondary hypertension and helps illustrate the role of vasoconstriction versus volume. Overall the incidence is about 5%. But higher in specialty centers, Renovascular hypertension is the consequence of narrowing of renal artery leading to renal artery stenosis.

B. The classic model of renovascular hypertension is what was produced experimentally as “Goldblatt hypertension” in the dog when a clip was placed on one renal artery leading to
constriction on that side (so called one clip two kidney model) and helped clarify some aspects pathogenesis of hypertension. The hypertension produced was initiated by reduction of perfusion pressure of the clipped kidney which resulted in excessive renin production by that kidney. The reduced perfusion pressure will lead the ischemic kidney to retain Na and water, thereby increasing volume. The contralateral kidney responds to elevated perfusion pressure caused by hypertension by increased salt and water excretion from the non stenotic kidney. The plasma volume, therefore, remains normal but it is not enough to normalize the blood pressure. The BP remains elevated maintained by vasoconstriction by renin-angiotensin system.

C. The human counterpart of the Goldblatt hypertension is unilateral renal artery stenosis with normal contralateral kidney. However, if there is only one kidney which has renal artery stenosis or if there is stenosis of both renal arteries the mechanism changes. Even though the hypertension might have been started by increased renin secretion, it is maintained by increased volume because of the inability of kidneys to excrete sodium and water to restore volume. In solitary kidney absence of contralateral normal kidney and in bilateral kidneys both stenotic hence nonresponsive to increased pressure to induce pressure diuresis.

D. In unilateral renal artery stenosis with normal contralateral kidney blocking, the effects of renin-angiotensin system by such drugs as angiotensin converting enzyme inhibitors (ACEI) or similar drugs which block the action of angiotensin (ARBs or DRI) will be very effective. This is not the case in the two other types of renovascular hypertension where one would require to take care of volume by using diuretics. If there is either renal artery stenosis in a solitary kidney, such as a transplanted kidney or if there is bilateral renal artery stenosis, the elevated blood pressure is more volume dependent even thought he initiating factor might have been the increased renin secretion. This is due to the absence of other kidney in case of renal artery stenosis in solitary kidney and absence of pressure natriuresis. Similarly in situation where there is renal artery stenosis of both kidneys the pressure natriuresis effect is not evident and volume increases. Here use of a diuretic to reduce the volume is very important.

E. The role of volume in causing hypertension is further illustrated by chronic kidney disease. In patients with advanced kidney disease of any etiology, there is inability to excrete sodium and water. As volume increases, hypertension gets worse. Kidney disease in early stages may not associated with hypertension but as they progress and glomerular filtration rate drops they progressively develop hypertension and generally require increased dose of diuretics to control hypertension. When they are reach end-stage renal disease (ESRD) and are started on dialysis and fluid is removed, the blood pressure tends to return to normal.

F. Monogenic Hypertension; eight genes have been identified so far that results in hypertension. (Classic reference, Lifton, Cell 104 545-556;2001). All of these genetic defect or mutation leads to enhanced tubular sodium reabsorption (impaired natriuresis) and result in salt sensitive hypertension. The variability affected by these mutations is mediated through circulating mineralocorticoid hormones. The major regulator of the epithelium sodium channel (ENaC) activity in the collecting duct is mineralocorticoid receptor and its steroid hormone ligand aldosterone. This will not be discussed in this lecture.
V. Hypertensive Target Organ Damage to the Kidneys

1. The kidneys are both villain and victim of hypertension. They play a role in regulating hypertension and at the same time are victim of hypertension. Hypertension remains a major cause for kidney disease.

2. Two patterns of injury are seen in hypertension: Essential and Malignant

**Essential Hypertension** leads to hypertensive nephrosclerosis and is also known as benign nephrosclerosis. In early stages of hypertension, there is no histological abnormality noticed in kidneys. But over the course of time, there is gradual loss of nephron mass with progressive reduction of kidney size caused by cortical atrophy and fibrosis. This is secondary to afferent arteriolar hyalinization. A vast majority of patients with essential hypertension don’t develop end stage kidneys disease. That is believed in large part due to preservation of auto-regulation of renal blood flow. Whether there is an underlying genetic predisposition is unclear at this time.

Hypertensive nephrosclerosis is due to arteriolar hyalinization leading to ischemic injury resulting in nephrosclerosis. That is characterized by decrease in nephron mass, cortical atrophy and fibrosis with reduction in kidney size. Generally these patients give a long history of inadequately controlled blood pressure. It is more common in African American populations and whether there is genetic predisposition for hypertensive injury in this group is an active field of research.

**Malignant Hypertension** is the other pattern of injury seen with hypertension. It is a distinct clinical and pathology entity characterized by marked elevation of BP and evidence of widespread acute arteriolar injury. The presence of hypertensive neuroretinopathy (flame shaped hemorrhages, cotton wool exudates and very often papilledema) is essential to make a diagnosis. The injury is hypertensive vasculopathy seen as necrotizing arteriolitis in the central nervous system, kidneys, heart, and other organs. The pathology is very specific characterized by fibrinoid necrosis of afferent arterioles, intimal thickening of interlobular arteries with proliferative endarteritis, endarteritis fibrosa and onion-like lesions. Malignant hypertension causes injury by disrupting autoregulation of renal blood flow blood flow and transmission of direct pressure injury to blood vessels.

**Autoregulation in the pathophysiology of hypertension.** The pathophysiology of these two hypertensive injuries is different. In essential hypertension, the prominent lesion is glomerular ischemia secondary to arteriolar hyalinization and atherosclerosis. In contrast, the injury in malignant hypertension is very acute and appears to be directly related to pressure (barotraumas). The difference in these two kinds of injury can be understood in context of renal auto regulatory mechanisms. In essential hypertension the auto regulation of the kidneys is intact and the pressure is not transmitted to the glomerular capillaries. In malignant hypertension, the blood pressure exceeds the auto regulatory ceiling (200mmHg) and this pressure is directly transmitted. The renal auto regulation is maintained between mean arterial pressure of 60-80 mm to 180-200 mm. The auto regulation also maintains glomerular filtration rate (GFR). The auto regulation is mediated by increasing resistance in preglomerular afferent arterioles. The auto regulatory increase in afferent resistance not only maintains the constancy of blood flow and thus glomerular filtration but prevents
the increase pressure from being transmitted downstream to the capillaries. Thus in essential hypertension the auto regulation is preserved whereas in malignant hypertension it is lost. It is also important in other aspects of clinical practice. Certain disease states notably diabetes may have impaired kidney auto regulation right form an early stages and thus more prone to hypertensive injury. Some antihypertensive drugs, namely dihydropyridine class of calcium channel blockers disrupt renal auto regulation and must be used with caution in treating hypertension in presence of significant kidney disease.

The concept of autoregulation is an important one as it helps understand many clinical conditions and may help to tailor the mode of therapy. For example, in diabetic hypertensive patients autoregulation is lost – thus making the kidneys prone to hypertensive injury even in patients with controlled hypertension. The risk can be minimized by keeping blood pressure lower than in the non-diabetic patient.

Summary

- Kidneys are the prime effector organ for volume homeostasis.

- Kidneys are the prime source for enzyme renin which converts to angiotensin II through intermediate pathways.

- It has been long postulated that “essential hypertension is due primarily to an abnormal kidney (functionality) which has unwillingness to excrete sodium”. (Classic reference, de Wardner, J Hypertension 1996:14:S9-18)

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

- There is shifting of pressure natriuresis curve to right in essential hypertension.

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

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

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

- Kidneys are prone to hypertensive injury and keeping blood pressure under control prevents development of renal failure.
Abbreviations used in the handout:

**ACEI** = angiotensin converting enzyme inhibitor

**ARB** = angiotensin receptor blocker

**BP** = blood pressure

**CO** = cardiac output

**DBP** = diastolic blood pressure

**DRI** = direct renin inhibitor

**ECF** = extracellular fluid

**ECV** = extracellular volume

**EDCF** = endothelium-derived constricting factor

**EDRF** = endothelium-derived relaxing factor

**ENaC** = epithelium sodium channel

**ESRD** = end-stage renal disease

**GFR** = glomerular filtration rate

**HR** = heart rate

**HTN** = hypertension

**JG** = juxta-glomerular

**MAP** = mean arterial blood pressure

**Na** = sodium

**SBP** = systolic blood pressure

**SNS** = sympathetic nervous system

**SV** = stroke volume

**SVP** = systemic vascular pressure

**SVR** = systemic vascular resistance

**TPR** = total peripheral resistance