Essential Hypertension – Pathogenesis and Pathophysiology

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Population studies suggest the blood pressure (BP) is a continuous variable, with no absolute dividing line between normal and abnormal values1. High blood pressure is a leading risk factor for heart disease, stroke, and kidney failure. This correlation is more robust with systolic than with diastolic BP2. Even when BP is lowered by antihypertensive medication, the associated reduction in the incidence of coronary heart disease lags behind that of stroke3.

There is a widely held misconception that hypertension is a single disease that can be treated with a single recipe. Hypertension is a heterogenous disorder in which patients can be stratified by pathophysiologic characteristics that have a direct bearing on the efficacy of specifically targeted antihypertensive medications, on the detection of potentially curable forms of hypertension, and on the risk of cardiovascular complications4.

Essential hypertension is characterised by a sustained systolic pressure of greater than 140 mm Hg and a diastolic BP at greater than 90 mm Hg and by some characteristics listed in Table I.

The pressure required to move blood through the circulatory bed is provided by pumping action of the heart (cardiac output; CO) and the tone of the arteries (peripheral resistance; PR). Each of these primary determinants of the blood pressure is, in turn, determined by the interaction of the "exceedingly complex series of factors" displayed in part in figure 1.

Hypertension has been attributed to abnormalities in virtually every one of these factors. It is unlikely that all of these factors are operative in any given patient; but multiple hypotheses may prove to be correct, since the haemodynamic hallmark of primary hypertension – a persistently elevated vascular resistance – may be reached through a number of different paths. Before the final destination, these may converge into either structural thickening of the vessel walls or functional vasoconstriction. Moreover, individual factors often interact, and the interactions are proving to be increasingly complex. For instance, insulin resistance is present even before hypertension develops in those who are genetically predisposed, the resultant hyperinsulinaemia is associated with sodium sensitivity, obesity, and increased sympathetic drive as well as impaired endothelium-dependent vascular resistance8.

Table I : Pathophysiologic characteristics of essential hypertension5.

| No known cause                                                                 |
| Diastolic pressure repeatedly > 90 mm Hg                                      |
| Total peripheral resistance usually increased                                  |
| Pulse pressure possibly increased or decreased                                |
| Cardiac output normal, or elevated in some, possibly early in the disease     |
| Cardiac work increased                                                         |
| Altered renal physiology, with accelerated natriuresis and reduced renal blood flow |
| Normal blood flow to most regions; diminished renal and skin blood flow and increased muscle flow may develop |
| Plasma volume reduced (may be inversely related to diastolic pressure)         |
| Hyper-reactivity of pressure to stress, abnormal vascular reactivity and impaired circulatory homeostasis |

Role of genetics

The variations in BP that are genetically determined are termed "inherited BP". Although, we do not
know which genes cause BP to vary, we know from family studies that inherited BP can range from low normal BP to severe hypertension. Although, it has frequently been indicated that the causes of essential hypertension are not known, this is only partially true because we have little information on genetic variations or genes that are over-expressed or under-expressed as well as the intermediary phenotypes that they regulate to cause high BP. Factors that increase BP, such as obesity and high alcohol and salt intake are called “hypertensinogenic factors”; some of these factors have inherited, behavioural, and environmental components. Inherited BP could be considered as the core BP, whereas hypertensinogenic factors cause BP to increase above the range of inherited BPs. Further, there are interactions between genetics and environmental factors that influence intermediary phenotypes such as sympathetic nerve activity, renin angiotensin aldosterone and renin - kallikrein - kinin systems and endothelial factors, which is turn influence other intermediary phenotypes such as sodium excretion, vascular reactivity, and cardiac contractility. These and many other intermediary phenotypes determine total vascular resistance and cardiac output and consequently BP.

The identification of variants (allelic) genes that contribute to the development of hypertension is complicated by the fact that the 2 phenotypes that determine BP, i.e., cardiac output and total peripheral resistance, are controlled by intermediary phenotypes, including the autonomic nervous system, vasopressor/vasodepressor hormones, the structure of the cardiovascular system, body fluid volume and renal function, and many others. Furthermore, these intermediary phenotypes are also controlled by complex mechanisms including BP itself. Thus there are many genes that could participate in the development of hypertension.

The influence of genes on BP has been suggested by family studies demonstrating associations of BP among siblings and between parents and children. There is better association among BP values in biological children than in adopted children and in identical as opposed to non-identical twins. BP variability attributed to all genetic factors varies from 25% in pedigree studies to 65% in twin studies. Furthermore, genetic factors also influence behavioural pattern, which might lead to BP elevation. For example, a tendency towards obesity or alcoholism will be influenced by both genetic and environmental factors, thus the proportion of BP variability caused by inheritance is difficult to determine and may vary in different populations.

Mutations in at least 10 genes have been shown to raise or lower BP through common pathways by increasing or decreasing salt and water reabsorption by the nephron. The genetic mutations responsible for 3 rare forms of mendelian (monogenic) hypertension syndromes - gluco-corticoid remediable aldosteronism (GRA), Liddle’s syndrome, and apparent mineralocorticoid excess (AME) have been identified, whereas in a fourth, autosomal dominant hypertension with brachydactyly the gene is not yet identified but has been mapped to chromosome 12. Subtle variations in one of these genes may also cause some forms of “essential” hypertension.

Polymorphisms and mutations in genes such as angiotensin gene, angiotensin converting enzyme, B2 adrenergic receptor, adducin, angiotensinase C, renin binding proteins, G-protein B3 subunit, atrial natriuretic factor, and the insulin receptor have also been linked to the development of essential hypertension; however, most of them show a weak association if any, and most of these studies need further confirmation.

**Cardiac output**

An increased cardiac output has been found in some young, borderline hypertensives who may display a hyperkinetic circulation. If it is responsible for the hypertension, the increase in cardiac output could logically arise in two ways: either from an increase in fluid volume (preload) or from an increase in contractility from neural stimulation of
the heart (Fig 1). However, even if it is involved in initiation of hypertension, the increased cardiac output likely does not persist, since the typical haemodynamic finding in established hypertension is an elevated peripheral resistance and normal cardiac output.13

Significant increases in left ventricular mass have been recognised in the still normotensive children of hypertensive parents.14,15 Such ventricular hypertrophy has generally been considered a compensatory mechanism to increased vascular resistance (afterload). However, it could reflect a primary response to repeated neural stimulation and, thereby, could be an initiating mechanism for hypertension as well as amplifier of cardiac output that reinforces the elevation of BP upstream from the constricted arteriolar bed.17

An increased circulatory fluid volume (preload) could induce hypertension by increasing cardiac output. However, in most studies, patients with established hypertension have a lower blood volume and total exchangeable sodium than do normal subjects.18

**Autoregulation**

The pattern of initially high cardiac output giving way to persistently elevated peripheral resistance has been observed in a few people and many animals with experimental hypertension. When animals with markedly reduced renal tissue are given volume loads, the blood pressure rises initially as a consequence of the high cardiac output but within a few days, peripheral resistance rises, and the cardiac output returns to near basal levels.19

This changeover has been interpreted as reflecting an intrinsic property of the vascular bed to regulate the flow of blood, depending on the metabolic need of tissues. This process, called autoregulation, has been described and demonstrated experimentally.20 With increased cardiac output, more blood flows through the tissues than is required, and the increased flow delivers extra nutrients or removes additional...
metabolic products; in response, the vessels constrict, decreasing blood flow and returning the balance of supply and demand to normal. Thus the peripheral resistance increases and remains high by the rapid induction of structural thickening of resistance vessels.

Similar conversion from an initially high cardiac output to a later increased peripheral resistance has been shown in hypertensive people. But the role of autoregulation has been questioned by various reasons. These include the finding that patients with increased cardiac output also have increased oxygen consumption rather than lower level that should be seen if there was overperfusion of tissues, as entailed in autoregulation concept. Nonetheless, the auto-regulatory model does explain the course of hypertension, in volume expanded animals and people, particularly in the presence of reduced renal mass.

Excess sodium intake
Excess sodium intake induces hypertension by increasing fluid volume and preload, thereby increasing cardiac output. Sodium excess may increase blood pressure in multiple other ways as well; affects vascular reactivity and renal function. Diets in non-primitive societies contain many times the daily adult sodium requirements, an amount that is beyond the threshold level needed to induce hypertension. Only part of the population may be susceptible to the deleterious effects of this high sodium intake, presumably because these individuals have an additional renal defect in sodium excretion.

Epidemiologic evidence
The epidemiologic evidence incriminating an excess of sodium goes as follows:

- Primitive people from widely different parts of the world who do not eat sodium have no hypertension, nor does their BP rise with age, as it does in all other industrialised populations.
- If primitive people who are free from hypertension adopt modern life styles, including increased intake of sodium, then their BP rises and hypertension appears.
- In population studies, a significant correlation between the level of salt intake and frequency of hypertension has been found. In the Intersalt study, which measured 24-hours urine electrolytes and BP in 10,079 men and women aged 20 to 59 in 52 places around the world, there was a positive correlation between sodium excretion and both systolic blood pressure (SBP) and diastolic blood pressure (DBP), but a more significant association between sodium excretion and the changes in BP with age.

Experimental evidence

- When hypertensive patients are on sodium restricted diet, their BP falls.
- Short periods of increased NaCl intake has been shown to raise BP in normotensives, especially genetically predisposed animals.
- In randomised controlled studies of hundreds of patients with high normal blood pressure, those patients who moderately restricted their sodium intake for 36 months to 5 years, had lower blood pressure and a decreased incidence of hypertension than did the patients who did not reduce their sodium intake.
- A high sodium intake may activate a number of pressure mechanisms, viz., increases in intraacellular calcium and plasma catecholamines, worsening of insulin resistance, and a paradoxical rise in atrial natriuretic peptide.

Sensitivity of sodium

Since almost everyone in western countries ingests a high sodium diet, the fact that only about half will develop hypertension suggests a variable degree of blood pressure sensitivity to sodium. Although, obviously both heredity and interactions with other environmental exposures may be involved, Weinberger et al defined sodium
sensitivity as a 10mm Hg or greater decrease in mean blood pressure from the level measured after 4 hour infusion of 2 L normal saline compared to the level measured the morning after 1 day of a 10 mmol sodium diet, during which three oral doses of furosemide were given at 10 AM, 2 PM, and 6 PM. Using this criteria they found that 51% of hypertensives, but only 26% of normotensive were sodium sensitive. Multiple mechanisms of sodium sensitivity has been proposed, viz., defect in renal sodium excretion, increased activity of the sodium hydrogen exchanger, increased sympathetic nervous system activity, increased calcium entry into vascular smooth muscle, impaired nitric oxide synthesis. Blacks have greater frequency of salt sensitivity. Salt sensitivity increases with age, and perhaps more in women than in men. In a recent study Fujiwora et al reported that modulation of NO synthesis by salt intake may be involved in a mechanism for salt sensitivity in human hypertension.

Altered renal physiology

In essential hypertension, physiologic and pathologic renal changes often precede changes identifiable in other organs, but whether they precede or follow the onset of the hypertension itself has not been determined. The earliest physiologic lesion of essential hypertension is vascular, GFR is maintained; whereas total renal blood flow is reduced (increased filtration fraction). This pattern may be explained by diffuse, predominantly efferent but also afferent, vasoconstriction of all nephrons or, alternatively, by selective afferent vasoconstriction with diversion of blood away from some nephrons to maintain near normal GFR. This renal vasoconstriction is reversible and could lead to reduced pressure and flow in the post glomerular circulation, which may predispose to increased tubule Na+ reabsorption.

Abnormal renal sodium transport

Body volume varies directly with total body Na+, because Na+ is the predominant extracellular solute that retains water within the extracellular space. One primary function of the kidneys is to regulate Na+ and water excretions, and consequently, they play a dominant role in the long term control of BP. To achieve this goal, two important renal mechanisms are utilised. One mechanism regulates extra cellular fluid volume by coupling increases or decreases in urinary excretion of Na+ and water, and the related changes in renal perfusion pressure. This phenomenon has been referred to a pressure natriuresis and pressure diuresis (Fig. 2).

The second mechanism employs the renin-angiotensin - aldosterone system, which directly controls peripheral vascular resistance and renal reabsorption of Na+ and water.

Renal sodium retention

Essential hypertension is due primarily to an abnormal kidney which has an unwillingness to excrete sodium.

Various investigations have proposed different hypotheses to explain for abnormal renal sodium retention as the initiating event for hypertension.

Resetting of pressure natriuresis

Guyton considers the regulation of body fluid volume by the kidneys to be the dominant mechanism for the long term control of blood pressure, the only one of many regulatory controls to have sustained and infinite power. Therefore, if hypertension develops, something must be amiss with the pressure natriuresis control mechanism or else the BP would return to normal.

Under normal conditions, the perfusion pressure is around 100 mm Hg, sodium excretion is about 150 mEq/day, and these two mechanisms are in a remarkably balanced state. The curve relating arterial pressure to sodium excretion is steep. As Guyton and co-workers have shown, either the entire curve can be shifted to the right or the slope can be depressed, depending on the type of renal insult, which intum, is reflected by varying sensitivity.
Cross transplantation studies in animal models and in humans have shown that the alteration in renal function responsible for the resetting of the pressure natriuresis curve is inherited.

Reduced nephron number

Brenner et al advanced the hypothesis that the nephron endowment at birth is inversely related to the risk of developing hypertension later in life. The congenital reduction in the number of nephrons or in the filtration surface area (FSA) per glomerulus, limits the ability to excrete sodium, raises the blood pressure, and setting off a vicious circle, whereby systemic hypertension begets glomerular hypertension which begets more systemic hypertension (Fig. 3).

These investigators point out that as many as 40% of individuals under age 30 have fewer than the presumably normal number of nephrons (600,000 per kidney) and “speculate that those individuals, whose congenital nephron numbers fall in the lower range, constitute the population subsets that exhibit enhanced susceptibility to the development of essential hypertension”. Similarly, a decrease in filtration surface, reflected in a decreased glomerular diameter or capillary basement membrane surface area may be responsible for an increased susceptibility to hypertension even in the presence of a normal nephron number.

The congenital decrease in filtration surface has been put forward as a possible explanation for observed differences in susceptibility to hypertension among genetic populations as well as in blacks, women, and older people, all of whom may have smaller kidneys or fewer functioning nephrons.
Acquired natriuretic hormone

The Guyton hypothesis allows for a normal blood volume despite an elevated pressure, in keeping with most volume measurements in hypertensive patients. The next hypothesis requires an initially expanded plasma volume that, after an inhibition of renal sodium reabsorption, is allowed to return to normal.

Ouabain, an endogenous digitalis like inhibitor of sodium pump, which arises when plasma volume is expanded, increases intracellular sodium and mobilises calcium from intracellular stores. Blaustein has formulated an overall scheme for this acquired compensatory mechanism for renal sodium retention, which could be a cause of essential hypertension (Fig. 4).

Renin-angiotensin - aldosterone system

Renin may play a critical role in the pathogenesis of most hypertension, a view long espoused by Laragh.

Fig. 4: Diagram showing various feedback loops that may be involved in the rise in blood pressure that accompanies the attempt to prevent plasma volume expansion when excessive sodium is ingested relative to the innate ability of the kidneys to excrete a sodium load. The increase in intracellular sodium is the direct result of the inhibition of the Na⁺ pump by ouabain; the increase in intracellular calcium is then mediated by the Na⁺/Ca²⁺ exchanger as a result of the rise in sodium. (+) positive feedback loop; (−), negative feedback loop; ADH antidiuretic hormone; ANP, atrial natriuretic peptides; [Na⁺]i, intracellular sodium concentration; [Ca²⁺]i, intracellular calcium concentration.
Fig. 5 is a schematic overview of the renin-angiotensin system showing its major components, the regulators of renin release and the primary effects of angiotensin II (AII) excluding the AII receptors.

Although, low renin levels are expected in essential hypertension, the majority of patients with essential hypertension do not have low suppression renin angiotensin levels but “inappropriately” normal or even elevated PRA levels. Indeed, when renin profiling is correctly performed and indexed in patients with essential hypertension, about 20% are found to have high renin values, and about 30% have low renin values, with the remaining half distributed between these two extremes.

It seems likely that this mechanism is abnormally activated in many patients with essential hypertension, and at least three mechanisms have been offered: nephron heterogeneity, non-modulation, and increased sympathetic drive.

Nephron heterogeneity with unsuppressible renin secretion and impaired natriuresis as cause of essential hypertension:

Within the kidneys, there exists a functional and structural basis for the abnormal renin secretion...
and impaired Na+ excretion that are characteristic of hypertensive states54 (Table II)69.

Table II: Hypothesis - there is nephron heterogeneity in essential hypertension69.

1. There are ischaemic nephrons with impaired sodium excretion intermingled with adapting hyperfiltering hypernatriuretic nephrons.
2. Renin secretion is high from ischaemic nephrons and low from hyperfiltering nephrons.
3. The inappropriate circulating renin-angiotensin level impairs sodium excretion because:
   a. In the adapting hypernatriuretic nephrons
      i. It increases tubular sodium reabsorption.
      ii. It enhances tubuloglomerular feedback-mediated afferent constriction.
   b. As the circulating renin level is diluted by non-participation of adapting nephrons, it becomes inadequate to support efferent tone in hypoperfused nephrons.
4. A loss of nephron number with age and from ischaemia further impairs sodium excretion.

Non-modulation
This has been proposed by Williams and Hollenberg for normal renin and high renin levels seen in nearly half of hypertensive patients due to defective feed-back regulation of the renin-angiotensin system within the kidneys and the adrenal glands70.

Normal individuals modulate the responsiveness of their All target tissues with their level of dietary sodium intake. With sodium restriction, the adrenal secretion of aldosterone is enhanced and vascular responses are reduced, with sodium loading, the adrenal response is suppressed, and vascular response are enhanced, particularly within the renal circulation. With sodium restriction, renal blood flow (RBF) is reduced, facilitating sodium conservation; with sodium loading, RBF is increased, promoting sodium excretion. These changes are mediated mainly by changes in All level, increasing with sodium restriction and decreasing with sodium loading.

Non-modulation is characterised by abnormal adrenal and renal responses to All infusions and salt loads71. These findings have been attributed to an abnormally regulated and rather fixed level of All, that, in the adrenal tissues, does not increase aldosterone secretion in response to sodium restriction and, in the renal circulation, does not allow renal blood flow to increase with sodium loading. The hypothesis that there is an abnormally regulated, fixed local All concentration in these modulators received support from the correction of both the adrenal and renal defects after suppression of All by ACE-inhibitors.

Non-modulation in the face of relatively high dietary sodium intake could explain the pathogenesis of sodium sensitive hypertension and provide a more targeted, rational therapy for correction. Moreover, a lower prevalence of non-modulation has been found in young women, suggesting that female sex hormones may confer protection against this genotypic predisposition to hypertension72.

Low renin essential hypertension
Although low renin levels are expected in the absence of one or another of the previously described circumstances, a great deal of work has been done to uncover special mechanisms, prognoses, and therapy for hypertension with low renin.

The possible mechanisms for low renin hypertension include volume expansion with or without mineral corticoid excess but majority of careful analyses fail to indicate volume expansion73 or increased levels of mineralocorticoids74. Recent studies by Fishar75 et al focus on adrenal and pressure responsiveness to angiotensin II (ang. II) as a function of dietary salt intake in patients with low renin hypertension, normal renin hypertension, and normal controls. There were striking functional
similarities between normal renin hypertension and non-modulating essential hypertension with normal plasma renin activity, including:

(i) Salt sensitivity of the blood pressure,

(ii) blunted plasma aldosterone responses to ang.

III infusion and upright posture after 5 days of rigid dietary sodium restriction, and

(iii) relatively low basal plasma aldosterone levels.

These differences compared to normal controls and modulating hypertensive subjects disappeared when dietary salt intake was increased to 200 mEq/day, consistent with suppression of plasma ang. II activity during high salt intake with resensitization of ang. II receptors and improved ang. II responsiveness.

If so, perhaps the blunted responsiveness to ang. II during sodium restriction could reflect the continuing generation of ang. II, with angiotensin receptor down regulation in these subjects.

Mutations in the HSD II B2 gene causes a rare monogenic juvenile hypertensive syndrome called apparent mineralocorticoid excess (AME). In AME, compromised II. HSD enzyme activity results in over stimulation of the mineralocorticoid receptor (MR) by cortisol; causing sodium retention, hypokalaemia, and salt dependent hypertension76,77.

There is evidence that an impaired II hydroxysteroid dehydrogenase (II B HSD2 activity) type 2 may play a role in the

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<tr>
<th>High renin essential hypertension</th>
<th>Low renin essential hypertension</th>
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<tr>
<td>Renovascular and malignant hypertension</td>
<td>Primary aldosteronism</td>
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### Vascular sequelae

<table>
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<th>High</th>
<th>Low</th>
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<td>Stroke</td>
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<td>Heart attack</td>
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<td>Renal damage</td>
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<td>Retinopathy encephalopathy</td>
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### Treatments

<table>
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<td>Converting enzyme inhibitors</td>
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<td>Beta blockers</td>
<td>-</td>
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<td>Calcium channel blockers</td>
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<td>Diuretics</td>
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<td>Alpha blockers</td>
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The pathogenesis of essential hypertension in some patients and this may be genetically determined. Because 40% of patients with essential hypertension have low renin levels, a number of these patients may have a mild form of AME. Furthermore, as spironolactone causes ready remission, it is important to seek the diagnosis by genetic and clinical studies. The prevalence of mutations of II HSD2 in general population of patients with essential hypertension is presently unknown. The epidemiology of such mutations is relevant for two reasons. First, the prevalence is important in order to define the cost-benefit ratio for screening patients with low renin-low aldosterone hypertension. Second, the accurate diagnosis of AME should permit the design of more specific therapies for patients with this disease\textsuperscript{76,77}.

Two forms of vasoconstriction in essential hypertension:

Two forms of vasoconstriction, one mediated by renin and other by Na\textsuperscript{+} - volume forces, seen in extreme forms of hypertension also operate in essential hypertension. Laragh and co-workers\textsuperscript{78,79} have long attached a great deal of significance to various PRA levels found in patients with essential hypertension. According to this view, the levels of renin can identify the relative contribution of vasoconstriction and body fluid expansion to pathogenesis of hypertension. According to the “bipolar vasoconstriction - volume analysis,” arteriolar vasoconstriction by AII is predominantly responsible for the hypertension in patients with high renin, whereas volume expansion is predominantly responsible in those with low renin. Though, both lead to increased peripheral resistance, which is the common characteristic of all hypertension. The similarity ends there, however, because the conditions imposed by these two agents are radically different in their implications for risk, survival, and treatment (Fig. 6)\textsuperscript{80}.

### The Laragh vasoconstriction – volume spectrum of clinical hypertension

<table>
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<tr>
<th>PRA</th>
<th>Vasoconstriction</th>
<th>Body Na\textsuperscript{+}</th>
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<tr>
<td>High</td>
<td>Malignant hypertension&lt;br&gt;Unilateral renovascular&lt;br&gt;High renin essential hypertension&lt;br&gt;Pheochromocytoma</td>
<td>Low</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium-renin essential hypertension&lt;br&gt;Bilateral renovascular hypertension</td>
<td>Normal</td>
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<tr>
<td>Low</td>
<td>Low-renin essential hypertension&lt;br&gt;Primary hyperaldosteronism</td>
<td>High</td>
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Normal BP = (PRA) X (Na\textsuperscript{+} → Volume)

Fig. 7: The spectrum of hypertensive disorders stratified according to their renin-sodium relationship. Normal subjects, as indicated by the equation at the bottom of the figure, maintain and defend normotension by curtailing renal renin secretion in reaction to a rise in sodium intake or autonomic vasoconstriction, or by proportionally increasing renin secretion in the face of either Na\textsuperscript{+} depletion or hypertension from fluid or blood loss or a neurogenic fall in blood pressure. Hypertensive subjects sustain their higher blood pressures by renal secretion of too much renin for their Na\textsuperscript{+} volume states, or by renal retention of too much Na\textsuperscript{+} (Volume) for their renin level, which often fails to fully turn off as it does in normal subjects. High renin hypertensive patients are proportionately more vasoconstricted with poor tissue perfusion and therefore most susceptible to cardiovascular tissue ischaemic damage. BP = blood pressure; PRA = plasma renin activity.
The predominance of activity of either pole depresses activity at other, whereas both vasoconstrictive forces may well assert their influence when renin levels are in the medium range.

**Human hypertensive disorders as a spectrum of abnormal plasma renal-sodium volume products**

Normotension is sustained and defended by fluctuation of PRA according to salt intake and Na+ balance. Human hypertensive states are characterised by excessive renal renin secretion and thus PRA for the concurrent state of Na+ balance (i.e., by a spectrum of abnormally high plasma renin levels) for the Na+ -volume status or vice versa, i.e., renal retention of too much Na+ (Volume) for their renin level which often fail to fully turn off as it does in normal subjects69 (Fig. 7).

**Stress and sympathetic overactivity**

As shown in Figure 1 an excess of renin-angiotensin activity could interact with the sympathetic nervous system (SNS) to mediate most of its effects. On the other hand, stress may activate the SNS directly; and SNS overactivity in turn, may interact with high sodium intake, the renin-angiotensin system, and insulin resistance among the other possible mechanisms. Considerable evidence, supports increased SNS activity in early hypertension and, even more impressively, in the still normotensive offspring of hypertensive parents, among whom a large number are likely to develop hypertension.

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![Fig. 8: Indications that an increased sympathetic outflow may be key factor in primary hypertension. The outflow is increased when arterial baroreceptors are reset so that they exert less inhibition on the vasomotor center. The resetting could be due to genetic changes in the endothelial lining of the carotid sinus and aortic arch and/or at the vasomotor centers. The increased sympathetic outflow may be further enhanced by stress. As a consequence of this neurohumoral excitation, the systemic vascular resistance is increased. In addition, the endothelial cells in the resistance blood vessel may secrete less vasodilator and more vasoconstrictor substances, thus compounding the vasoconstriction. Furthermore, mitogens produced in endothelial cells and also released from platelets, together with norepinephrine, can cause proliferation of the vascular smooth muscle with a further aggravation of the systemic vasoconstriction](image-url)
Baroreceptor dysfunction

The baroreceptors when activated by a rise in BP or central venous pressure, respectively, normally reduce heart rate and lower blood pressure by vagal stimulation and sympathetic inhibition. When hypertension is sustained, these reflexes are reset rapidly from both structural and functional changes so that given increase in BP evokes less decrease in heart rate. Shepherd postulates that the decreased inhibition of the vasomotor center resulting from resetting of arterial baroreceptors (mechano receptors) may be responsible for increased sympathetic outflow and thereby in the perpetuation of hypertension.

Stress: People exposed to repeated psychogenic stresses may develop hypertension more frequently than otherwise similar people not so stressed.

- The blood pressure remained normal among nuns in a secluded order over a 20 years period, whereas it rose with age in women living nearby in the outside world.
- Annual rate of developing hypertension is 5.6 times greater among air traffic controllers, who work under high level of psychological stress, than non professional pilots.
- Among healthy employed men, job strain (defined as high psychological demands and low decision latitude on the job) is associated with 3.1 times greater odds ratio for hypertension, an increased left ventricular mass index by echocardiography, and higher awake ambulatory blood pressure.
- People may become hypertensive not just because they are more stressed, but because they respond differently to stress. Greater cardiovascular and sympathetic nervous reactivities to various laboratory stresses have been documented in hypertensives and in normotensive at higher risk of developing hypertension, extending even to a greater anticipatory BP response while awaiting an exercise stress test.
- Despite the rather impressive body of literature, the role of mental stress in the development of hypertension remains uncertain. Its effects are likely to depend on an interaction of at least three factors: the nature of the stressor, its perception by the individual, and the individual’s physiological susceptibility.

The role of acquired tubulointerstitial disease in the pathogenesis of salt dependent hypertension

It proposes that hypertension has two phases: an early phase in which elevations in blood pressure (BP) are mainly episodic and are mediated by a hyperactive SNS or RAS, and a second phase in which BP is persistently elevated and that is primarily mediated by an impaired ability of the kidney to excrete salt, NaCl. The transition from the first phase to the second occurs as a consequence of catecholamine induced elevations in BP that preferentially damage regions of the kidney (juxtamedullary and medullary regions) that do not autoregulate well to changes in renal perfusion pressure.

This may be the major mechanism for the development of salt-dependent hypertension, and particularly for the hypertension associated with blacks, aging, and obesity. Thus, essential hypertension may be a type of acquired tubulointerstitial renal disease.

Hypertension may result from entry into the pathway at other stages:

i Interstitial damage due to other mechanisms: Hypercalcaemia, chronic pyelonephritis, obstruction, heavy metals (lead), radiation, or associated with gout.
ii Mechanisms that directly compromise renal medullary blood flow: Cyclosporine, analgesic abuse, genetic reduction in medullary blood flow in spontaneously hypertensive rats (SHR).
iii Directly resulting in decreased sodium excretion.

Liddle’s syndrome, glucocorticoid - remediable aldosteronism, and the syndrome of apparent mineralocorticoid excess, and a genetic reduction...
in nephron numbers.

In conclusion, this hypothesis links early, episodic, salt independent hypertension with the later development of a persistent salt dependent hypertension with the new concept that it is mediated by acquired tubulointerstitial and peritubular capillary injury. A strength of the hypothesis is that it unites many prior hypotheses into one pathway; including that of Julius on the role of the sympathetic nervous system in early hypertension\(^93\), of Cowley \textit{et al} on the role of medullary ischaemia\(^94\), of Sealey and Laragh on activation of the renin-angiotensin II system\(^69\), of Guyton \textit{et al} on impaired pressure natriuresis\(^84\), of Kurokawa on enhanced TG feedback\(^95\) and Mackenzie, Lawler and Brenner on reduced nephron number\(^96\). In addition, it potentially provides answers to many questions not easily addressed by other individual hypothesis.

**Peripheral resistance**

Multiple factors affect peripheral resistance (Fig. 1). Main determinant of sustained elevated BP is increase in peripheral resistance which resides in precapillary vessels with a lumen diameter of less than 500 \(\mu\)m\(^97\). In human hypertension and in experimental animal models of hypertension, structural changes in these resistance vessels are commonly observed. In patients with essential hypertension, the characteristic findings include:

1. Decreased lumen diameter and,
2. Increased ratio of the diameter of vascular smooth muscle layer of the vessel (tunica media) to lumen diameter, referred to as the media to lumen ratio.

According to Poiseulle’s law, vascular resistance is positively related to both the viscosity of blood and the length of arterial system and negatively to the fourth power of the luminal radius. Since neither viscosity nor length are much, if at all, altered and the small change in luminal radius can have such a major effect, it is apparent that the increased vascular resistance seen in
established hypertension must reflect changes in the calibre of the small resistance arteries and arterioles.

The increase in media to lumen ratio of the resistance vessels occurs by the addition of material to the outer or inner surfaces of the blood vessel wall. This process requires growth (either hyperplasia or hypertrophy) of the cellular components of the blood vessel wall and results in an increase in its cross-sectional area. An alternative process, referred to as vascular remodelling, can result in an increased media to lumen ratio through the rearrangement of the existing material without an increase in the cross-sectional area of the vessel. For this to occur, a reduction in the external diameter of the blood vessel is required. In human essential hypertension, there is increasing evidence to support the view that vascular remodelling rather than growth, is the predominant change occurring in resistance vessels.

**Cell membrane alterations**

There is a body of evidence that shows that the cell membranes of hypertensive animals and, less

![Fig. 10: Hypotheses linking abnormal ionic fluxes to increased peripheral resistance through increase in cell sodium, calcium, or pH.](image)

![Fig. 11: A flow diagram illustrating the link between Na⁺/H⁺ exchanger activation and essential hypertension](image)
convincingly, of hypertensive people are altered in a primary manner, allowing abnormal movements of ions and thereby changing the intracellular environment to favour contraction and growth (Fig. 10)\(^9^9\). These primary alterations are differentiated from the secondary inhibition of the \(\text{Na}^+/\text{K}^+-\text{ATPase}\) pump by ouabain, which is secreted after volume expansion and, as described earlier, is a possible mechanism for renal sodium retention.

Abnormalities of the physical properties of the membrane and of multiple transport systems have been implicated in the pathogenesis of hypertension\(^1^0^0\). Most relate to vascular smooth muscle cells, but since such cells are not available for study in humans, surrogates such as red and white blood cells are used. Transport systems present in the cell membrane of erythrocytes that control the movement of sodium and potassium to maintain the marked differences in concentration of these ions on the outside and inside of cells, which in turn provides the electrochemical gradients needed for various cell functions\(^1^0^1,1^0^2\).

There is evidence that the sodium hydrogen exchanger is stimulated in hypertensive patients either by an increased cellular calcium load or enhanced external calcium entry. An increased \(\text{Na}^+/\text{H}^+\) exchanger could play a significant role in the pathogenesis of hypertension, both by stimulating vascular tone and cell growth and possibly by increasing sodium reabsorption in renal proximal tubule cells (Fig. 11)\(^1^0^4\).

RBC membranes from hypertensives have an increased cholesterol : phospholipid ratio in association with high sodium lithium transport (SLC)\(^1^0^5\) and increased ratios of fatty acid metabolites to precursors compared to those from age matched normotensives\(^1^0^6\). Such changes in lipids produce a high membrane microviscosity and decrease in fluidity\(^1^0^6\), which may be responsible for increased permeability to sodium and other alterations in sodium transport\(^1^0^7\).

**Endothelial dysfunction**

Nitric Oxide (NO) is the primary endogenous vasodilator (Fig. 12)\(^1^0^8\). Although, the role of NO in the regulation of BP is uncertain, several studies have reported its influence on BP and renal haemodynamics\(^1^0^9\). In healthy human subjects, inhibition of NO synthase by N-monomethyl-L-arginine acutely increased BP, peripheral vascular resistance, and fractional excretion of Na\(^+^1^1^0\).

NO is tonically active in the medullary circulation, so that reducing NO production or vascular responsiveness, reportedly enhances the pressure natriuresis response, followed by reductions in papillary blood flow, renal interstitial hydrostatic pressure, and Na\(^+\) excretion by almost 30\%, without corresponding changes in total or cortical RBF or GFR\(^1^0^9\). This mechanism may contribute to the blunted pressure natriuresis reported in experimental models.

**Endothelin**

Endothelin is among the
vasoconstrictors yet to be identified. Its actions are mediated through two types of receptors, \( \text{ET}_A \) and \( \text{ET}_B \), both of which are located on vascular smooth muscle. An orally active mixed endothelium receptor antagonist bosentan, reduced BP in hypertensive patients to a level that was comparable to enalapril\(^1\). Bosentan has also been reported to block the effects of an infusion of angiotensin II on BP and renal blood flow in rats\(^2\). This raises the issue of whether a component of these angiotensin II actions may be mediated by endothelin.

**Obesity**

Hypertension is more common in obese people. Obese individuals have higher cardiac output, stroke volume, and central and total blood volume and lower peripheral resistance than non-obese individuals with similar blood pressure\(^3\). The increase in cardiac output is proportional to the expansion of body mass and may be the primary reason for the rise in BP\(^4\). The prevalence of hypertension increased equally with increasing BMI, degree of upper body obesity, and fasting insulin levels\(^5\) (Fig. 13).

**Insulin resistance and hyperinsulinaemia**

Higher insulin levels are associated with more hypertension, and many possible mechanisms may explain the association. (Table III)\(^6\).

The hypertension that is more common in obese people may arise in large part from the insulin resistance and resultant hyperinsulinaemia that results from the increased mass of fat. However, rather unexpectedly, insulin resistance may also be involved in hypertension in non-obese people.
as well. The explanation for insulin resistance found in as many as half of non-obese hypertensive, however is not obvious and may involve one or more aspects of insulin’s action (Table IV).

Table III: Proposed mechanisms by which insulin resistance and/or hyperinsulinaemia may lead to increased blood pressure.

<table>
<thead>
<tr>
<th>Enhanced renal sodium and water reabsorption.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased blood pressure sensitivity to dietary salt intake</td>
</tr>
<tr>
<td>Augmentation of the pressure and aldosterone responses to All</td>
</tr>
<tr>
<td>Changes in transmembrane electrolyte transport</td>
</tr>
<tr>
<td>a. Increased intracellular sodium</td>
</tr>
<tr>
<td>b. Decreased Na+/K+ - ATPase activity</td>
</tr>
<tr>
<td>c. Increased intracellular Ca²⁺ pump activity</td>
</tr>
<tr>
<td>Increased intracellular Ca²⁺ accumulation</td>
</tr>
<tr>
<td>Stimulation of growth factors, especially in vascular smooth muscle.</td>
</tr>
<tr>
<td>Stimulation of sympathetic nervous activity</td>
</tr>
<tr>
<td>Reduced synthesis of vasodilatory prostaglandins</td>
</tr>
<tr>
<td>Impaired vasodilation</td>
</tr>
<tr>
<td>Increased secretion of endothelin</td>
</tr>
</tbody>
</table>

Effects of hyperinsulinaemia on blood pressure:

Figure 13, portrays three ways by which the hyperinsulinaemia that develops as a consequence of insulin resistance and reduced clearance could induce hypertension. Other mechanisms have been proposed (Table III). Of these, impaired endothelium-dependent vasodilation may be particularly important. Insulin normally acts as a vasodilator. It has been shown that although insulin increases sympathetic activity, the effect is normally overridden by the direct vasodilatory effect of insulin (Fig. 14).

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![Diagram](image)  
**Fig. 14**: The left panel represents insulin's action in normal humans. Although insulin causes marked increases in sympathetic neural out flow, which would be expected to increase blood pressure, it also causes vasodilation, which would decrease blood pressure. The net effect of these two opposing influences is no change or slight decrease in blood pressure. There may be an imbalance between the sympathetic and vascular actions of insulin in conditions such as obesity and hypertension. As shown in the right panel, insulin may cause potentiated sympathetic activation or attenuated vasodilation. An imbalance between these pressure and depressor actions of insulin may result in elevated blood pressure.
Table IV: Factors that may induce insulin resistance in hypertension.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Normal site of action</th>
<th>Effect of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin delivery</td>
<td>Capillary bed</td>
<td>Vasoconstriction; attenuated vasodilation, capillary rarefaction</td>
</tr>
<tr>
<td>Insulin transport</td>
<td>Interstitium</td>
<td>Impaired transport</td>
</tr>
<tr>
<td>Insulin action</td>
<td>muscle fibre</td>
<td>Genetic or acquired increase in type 2B fibres, hormonal interference with insulin effects, decreased transport protein</td>
</tr>
</tbody>
</table>

References


89. Sherwood A, Hindtlerl AL, Light KC. Physiological determinants of hyperreactivity to stress in border line


