HYPERTENSION

A Clinician's Guide to Diagnosis and Treatment

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DEDICATION

To our families

Preface

This book was developed for the busy clinician. It was designed to serve as a quick and up-to-date reference for physicians who evaluate and treat patients with *essential and secondary* hypertension. The manuscript was initially developed by one of the authors (BJS) to answer questions posed by clinicians at various symposia and lectures. With the aid of the coauthor, it subsequently grew into a book designed to meet the needs of clinicians who do not have time to look up specific clinical questions related to hypertension in encyclopedic textbooks.

This book is an accessible, quick and easy reference that makes available information on all facets of adult hypertension. Moreover, it provides references for detailed information about specific topics. The authors are grateful to the clinicians and academic nephrologists who reviewed and offered constructive criticisms of the text.

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Contents

CHAPTER 1

Clinical Physiology and Pharmacology of Blood Pressure Control

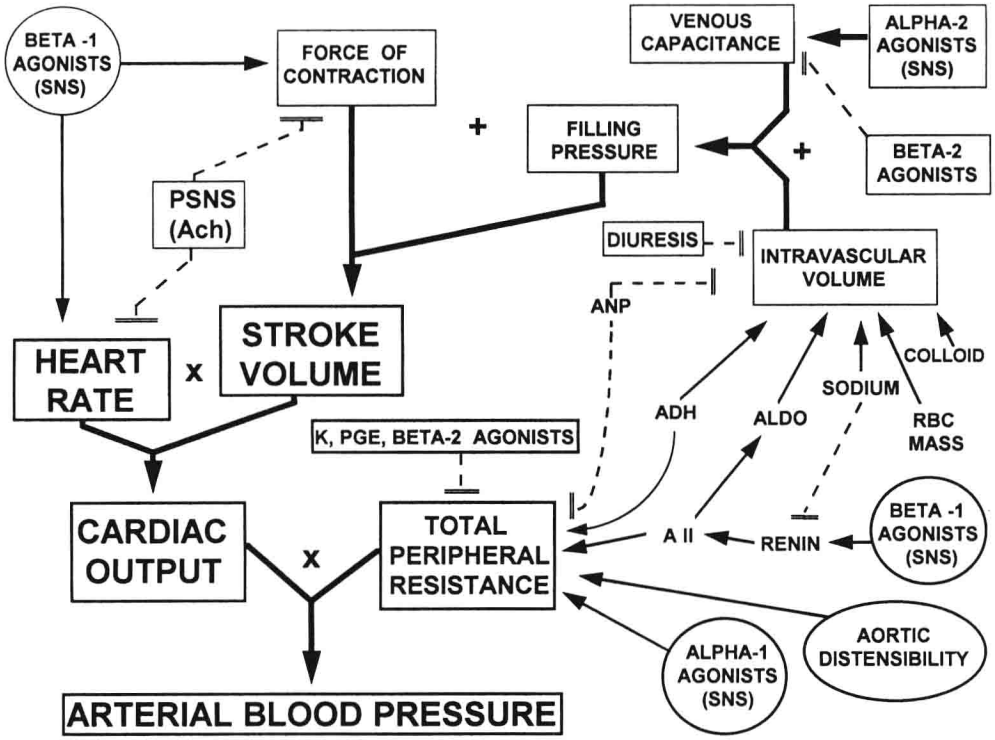

FIGURE 1. Factors responsible for arterial blood pressure. SNS = sympathetic nervous system; PNS = parasympathetic nervous system; Ach = acetylcholine; RBC = red blood cell; ADH = antidiuretic hormone; ALDO = aldosterone; → = stimulatory (positive) influence; ---|| = inhibitory (negative) influence; A I = angiotensin I; A II = angiotensin II; ANP = atrial natriuretic peptide; K = potassium; PGE = prostaglandin E.

I. **Clinical physiology of hypertension: a clinician's outline**

A. Factors responsible for arterial blood pressure (Fig. 1)

1. Blood pressure is determined by **cardiac output** and **peripheral resistance**.
2. Cardiac output depends on **heart rate** and **stroke volume**.
   a. **Heart rate** is governed by:
      i. **Beta-1 receptors** stimulated by the sympathetic nerves.
      ii. **Cholinergic receptors** governed by the parasympathetic nerves.
   b. **Stroke volume** is determined by:
      i. **Force of contraction** (also influenced by the autonomic stimuli).
      ii. **Filling pressure** determined by:
         (a) **Venous capacitance.**
         (b) **Intravascular fluid volume.**
3. Both peripheral resistance and intravascular fluid volume are influenced by **neural, humoral,** and **renal** factors.
   a. Note that renal mechanisms are responsible for long-term maintenance of arterial pressure, whereas neural mechanisms are responsible for immediate (though less complete) regulation. When the arterial setpoint is abnormally high, it is the renal-fluid mechanism which maintains that level and prevents unlimited long-term increases in arterial pressure.

B. Feedback loops in the regulation of arterial blood pressure (Fig. 2)
Because of their number and complexity, no attempt is made here to cover all feedback and reflex mechanisms. Rather, an overview of the clinically most relevant ones is presented. For further information, the reader is referred to appropriate reviews listed at the end of this chapter.[1,5,8]

1. **Rapid responses and reflexes** (seconds)
   a. A **rise** in arterial blood pressure causes the baroreceptor system to respond by inhibiting sympathetic output and stimulating parasympathetic output (via the vagus nerve) from the central vasomotor center in the brainstem. This results in:
      i. Decreased sympathetic outflow to arterioles (decreasing peripheral resistance).
      ii. Decreased sympathetic outflow to veins (decreasing cardiac filling pressure).
      iii. Decreased sympathetic tone to the heart (slowing heart rate and reducing contractility).
      iv. Increased parasympathetic tone to the heart (slowing heart rate and reducing contractility).
      v. Little change in antidiuretic hormone (ADH) secretion:
         (a) Baroreceptors tonically inhibit ADH secretion normally.
         (b) During hypotension this tone decreases, leading to increased release of ADH (vasopressin).
         (c) In cases of severe hypotension, the vasoconstrictor action of ADH becomes important (and rapid).
         (d) The antidiuretic effect of ADH is a component of the slower-acting responses and is not important in the rapid feedback mechanisms (*see* below).
   b. Although several pathways are activated in the baroreceptor arc, each limb (represented in Figure 2 by separate connections via the vagus and sympathetic fibers) is capable of being activated separately under certain circumstances.

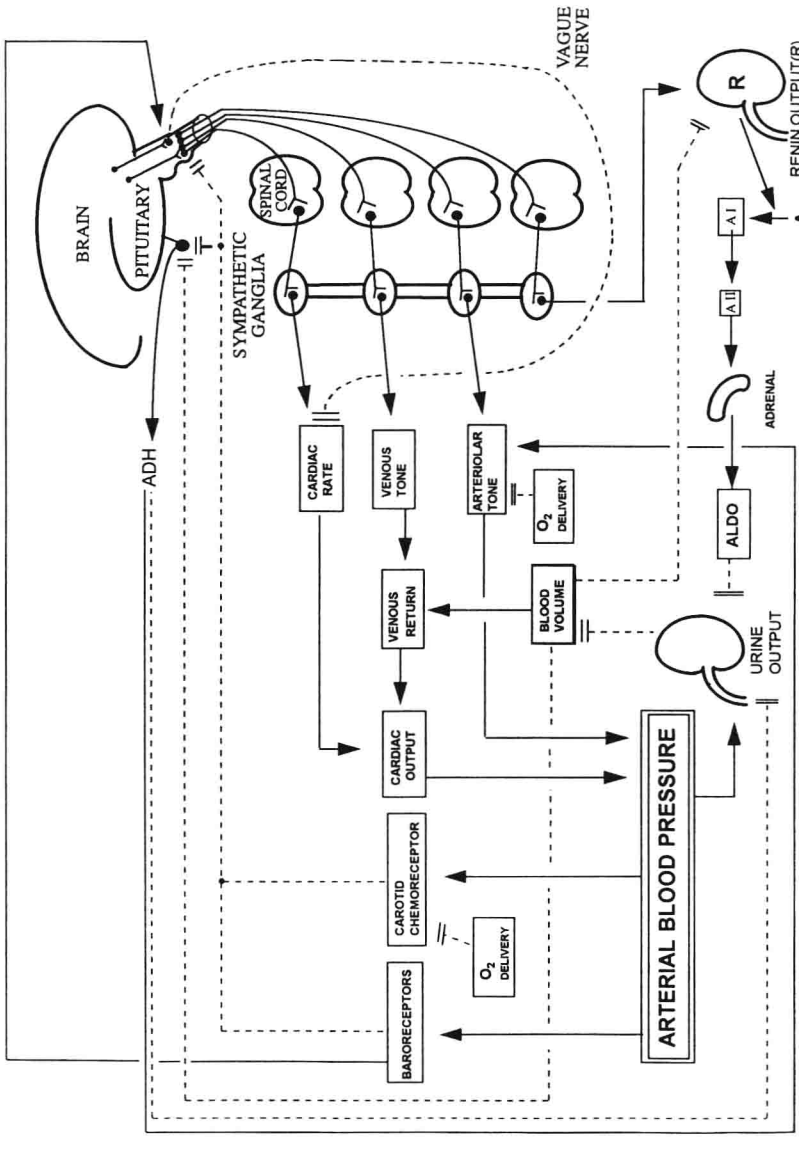

FIGURE 2. Feedback mechanisms in the control of blood pressure. ALDO = aldosterone; A = angiotensinogen; A I = angiotensin I; A II = angiotensin II; ADH = antidiuretic hormone; → = stimulatory (positive) influence; ⊣ = inhibitory (negative) influence.

c. **Chemoreceptors** also act at the vasomotor center but respond not only to arterial pressure but also to oxygen tension and carbon dioxide tension (in opposite directions). A **drop** in arterial pressure, a drop in oxygen tension, or a rise in carbon dioxide tension results in:
   i. Increased sympathetic outflow to skeletal arterioles.
   ii. Increased vagal tone, leading to slowing of heart rate.

d. The **central nervous system** (CNS, including supratentorial connections) itself senses ischemia or a rise in carbon dioxide in much the same way as the chemoreceptors do, and it can also influence the vasomotor center in various ways.

2. **Intermediate-acting responses** (minutes to hours)

a. **Renin-angiotensin system**
   i. Afferent arteriole baroreceptor causes renin release from the juxtaglomerular apparatus.
   ii. Macula densa mechanism
      (a) Renin secretion varies inversely with the chloride concentration reaching the thick ascending loop of Henle.[1]
   iii. Increased activity of the renal sympathetic nerves also increases renin release and often accompanies increased sympathetic outflow from other feedback loops.
   iv. Renin acts by converting angiotensinogen (synthesized in the liver) to angiotensin I.
   v. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE) (produced in the lungs).
   vi. Angiotensin II has two effects:
      (a) It is a potent vasoconstrictor (acting over minutes to hours).
      (b) It causes the adrenal gland to produce aldosterone over the next **several hours**; aldosterone action leads to volume expansion due to sodium retention.

b. **Antidiuretic hormone (ADH)**
   i. ADH secretion **increases in response to decreased blood volume** via a decrease in inhibitory tone from the **baroreceptors** to the hypothalamus.
   ii. A **rise in arterial pressure causes a decrease in secretion of ADH** related to increased baroreceptor activity, which normally inhibits hypothalamic ADH-releasing neurons.
   iii. Although increased secretion occurs in response to both increasing plasma osmolality and reduced intravascular volume, the response to rising osmolality is more immediate, while the response to reduced blood pressure (volume) is of greater magnitude.
   iv. ADH works by causing water conservation at the distal collecting duct of the nephron. This alone, without salt conservation, is a relatively inefficient mechanism of increasing intravascular volume, because water conserved is distributed among total body water and only a small portion of that is intravascular.

c. **Capillary filtration** (not shown)
   i. At higher arterial pressures, some fluid transudes across capillaries and into the interstitial space, reducing blood volume.

3. **Late-acting mechanisms** (days to weeks): Although these mechanisms take longer to activate, their long-term efficiency (gain) is greater than that with the shorter-acting systems.
   a. **Renal-body fluid system** (hours to days)
      i. A rise in arterial pressure leads to increased salt and water excretion directly (pressure diuresis).
      ii. ADH, in addition to acting as a pressor in the immediate response to severe hypotension and acting in the intermediate response to conserve blood volume, continues water conservation as long as the stimulus exists, and therefore is also a late-acting response as well.

C. Receptors mediating the control of blood pressure (Table 1)
   1. **Alpha-1 receptors**
      a. The peripheral postsynaptic receptor on the **arterioles:**
         i. Pressure is lowered by antagonism of this receptor.
   2. **Alpha-2 receptors**
      a. CNS synapse:
         i. **Stimulation is inhibitory** to the vasomotor output to arterioles, thereby **decreasing** peripheral neuron discharges and lowering peripheral resistance. Slowing of beta-1 output may also occur through the same mechanism at the heart.

TABLE 1. Receptors in the Modulation of Arterial Blood Pressure

Receptors	Agonist Actions	Agonists	Antagonists
Alpha-1	Vasoconstriction*	Norepinephrine >> dopamine > dolbutamine	Prazosin, labetalol
Alpha-2, central effect	Vasodilation	Clonidine, norepinephrine	
Alpha-2, peripheral effect	Venoconstriction	Clonidine, norepinephrine	
Alpha-1 and Alpha-2	Net vasoconstriction; reflex decreased cardiac output	Ergot, norepinephrine > epinephrine	Phentolamine, phenoxybenzamine
Beta-1	Increased cardiac output, lipolysis, increased renin	Epinephrine, norepinephrine, low-dose dopamine, dolbutamine†	Atenolol, metoprolol
Beta-2	Vasodilation,* bronchodilation	Albuterol, epinephrine >> norepinephrine	
Beta-1 and Beta-2	Net increased cardiac output	Epinephrine, isoproterenol	Propranolol, pindolol
Alpha-1 and Beta-1	Vasoconstriction and increased cardiac output	Epinephrine, high-dose dopamine	
Parasympathetic	Decreased cardiac output, decreased heart rate	Acetylcholine	Atropine

* Predominantly arteriolar.
† Without chronotropic effects (unlike dopamine and isoproterenol).

2. **Alpha-2 receptors** *(cont'd.)*
   b. Primary constrictor receptor on veins:
      i. Stimulation increases venous return.
      ii. The potential of increased venous return to cause increased cardiac output, and therefore higher pressure, is more than offset by arteriolar and cardiac effects due to baroreflexes in patients with an intact peripheral sympathetic nervous system.
3. **Beta-1 receptors**
   a. Heart:
      i. Stimulation results in increased heart rate.
      ii. Stimulation results in increased force of contraction.
   b. Kidney:
      i. Stimulation results in increased renin output.
4. **Beta-2 receptors**
   a. Arterioles: Stimulation results in relaxation.
   b. Bronchioles: Stimulation results in relaxation.

D. Neurotransmitters
1. **Epinephrine** (alpha-1, alpha-2 and beta-1, beta-2)
   a. Increase in heart rate
   b. No change or drop in blood pressure
2. **Norepinephrine** (alpha-1 and alpha-2 only)
   a. Hypertension without change in heart rate

E. Neurochemical interactions in the action of neuropharmacologic agents and blood vessel diameter (Fig. 3)
1. A blood pressure center within the brainstem is influenced by many forces, including baroreceptor feedback and supratentorial connections.
   a. Stimulation of central alpha-2 receptors inhibits alpha-1 and beta-1 output from the brainstem.
2. Neurons projecting from the brainstem synapse in the cord and those neurons, in turn, terminate in the sympathetic ganglia.
   a. Ganglionic blockers function at the sympathetic ganglia to block impulses there.
3. Electrical impulses cause the release of norepinephrine stored in granules.
   a. Guanethidine acts by replacing norepinephrine by incorporation into the granules, thereby depleting the stores of norepinephrine.
   b. Reserpine blocks the incorporation of neurotransmitter (norepinephrine) into granules.
4. After release from the presynaptic cell, norepinephrine attaches to the alpha receptors on the effector cells.
   a. Peripheral alpha-1 and nonselective alpha blockers prevent this.
5. After norepinephrine attaches to the effector alpha-1 receptor, a calcium channel activates the change in length of the muscle fibers.
   a. The uptake of calcium is blocked by calcium channel blockers.
6. Once norepinephrine reaches the extracellular cleft, it is removed by reuptake into the presynaptic cell and generalized metabolism via the blood stream.
   a. Reuptake is blocked by tricyclic antidepressants.
7. Norepinephrine also feeds back to alpha-2 receptors on the presynaptic nerve ending to lessen norepinephrine release.
   a. This action is blocked by nonspecific alpha blockers and alpha-2 blockers.

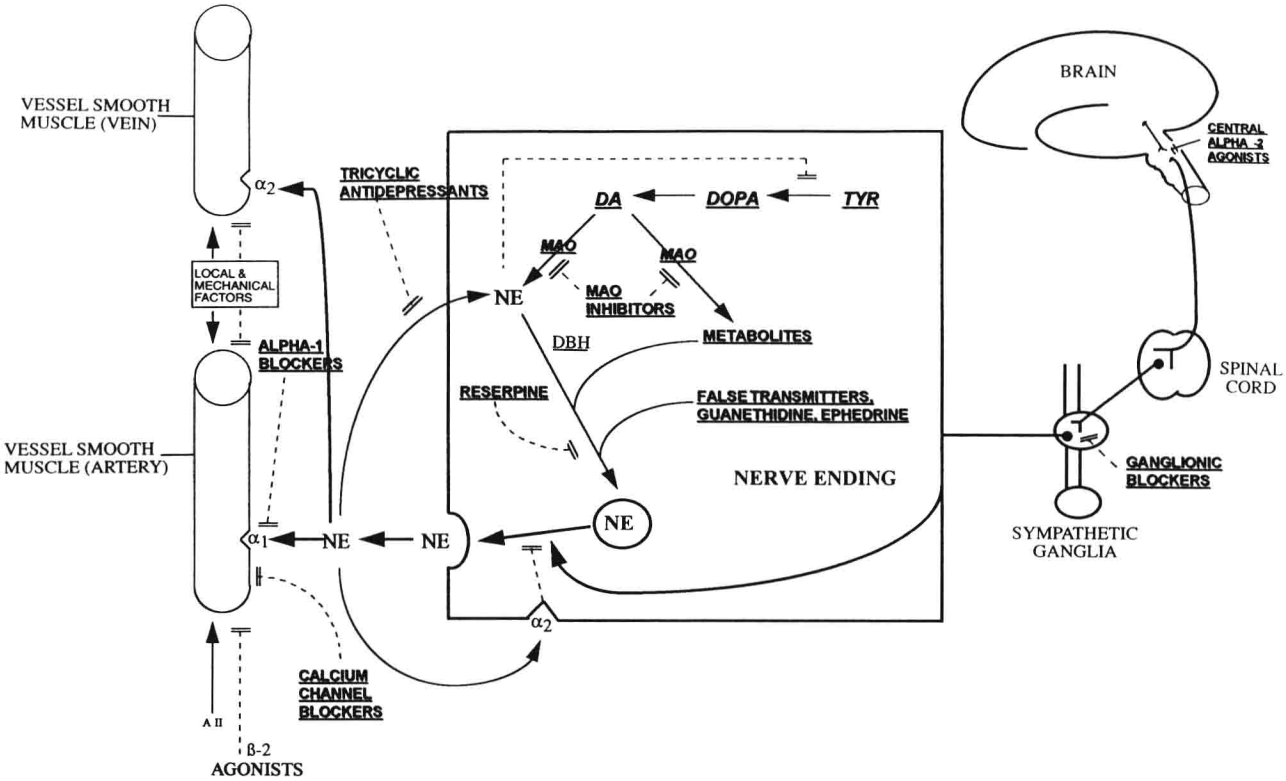

FIGURE 3. Neuropharmacologic interactions in the treatment of hypertension. A II = angiotensin II; NE = norepinephrine; TYR = tyrosine; DOPA = dihydroxyphenylalanine; DA = dopamine; MAO = monoamine oxidase; DBH = dopamine beta-hydroxylase; α_1 = α_1 receptors; α_2 = α_2 receptors; → = stimulatory (positive) influence; ---|| inhibitory (negative) influence.

II. **Mechanisms of antihypertensive drugs**

A. Central agents (alpha-2 agonists)

1. **Clonidine**
   a. Decreases sympathetic outflow to the beta-1 system receptors:
      i. Decreased cardiac output
      ii. Relative reduction in tendency of heart rate to rise
   b. Has little effect on alpha-1 receptor system:
      i. Baroreceptor reflexes are preserved.
      ii. Little change in peripheral resistance
   c. Acts directly on venous alpha-2 receptors to cause venoconstriction.
2. **Methyldopa**
   a. Decreases sympathetic outflow to the alpha-1 receptors of the arterioles, thereby reducing peripheral resistance with little (but some) effect on the heart. Some antinatriuretic effect occurs (probably due to some reduction in renal vascular resistance).
   b. Baroreceptor arc impaired because of action on arterioles.

B. Vasodilators

1. **"Direct" vasodilators** (hydralazine, diazoxide, minoxidil)
   a. Arteriolar effects only
   b. No direct cardiac effects; therefore, when used alone, direct vasodilators lead to reflex increases in heart rate and force of contraction.
   c. Require use of beta blockers and diuretics simultaneously in most cases.
2. **Calcium channel blockers**
   a. Arteriolar without venous dilation
   b. Relative impairment of cardiac conduction prevents reflex tachycardia.
   c. Have a slight natriuretic effect, and therefore total body sodium retention does not occur.
   d. Because arterioles are preferentially affected, transcapillary pressure increases, which may lead to local dependent edema, especially when cardiac output is not reduced.
   e. Drugs with greater cardiac depressant effects have lesser peripheral edema but a greater tendency toward increase in heart rate; drugs with less cardiodepressant effects lead to an increase in cardiac output and more peripheral edema.
3. **Alpha blockers**
   a. Nonselective
      i. Because they block both the postsynaptic receptor site *and* the presynaptic feedback site, catecholamine buildup within certain cells may lead to tachycardia due to release of catecholamines into the circulation with unopposed beta stimulation of the heart (tachycardia) and tachyphylaxis at other sites including the arterioles.
      ii. Nonselective inhibition of receptors in the gut leads to nausea, vomiting, and diarrhea.
   b. Selective alpha-1 blockers
      i. Block the action of norepinephrine at arteriolar receptors.
      ii. Selectivity prevents interference with feedback of norepinephrine and therefore no catecholamine buildup occurs.

C. Beta blockers
   1. Nonselective without instrinsic sympathomimetic activity (ISA)
      a. Central side effects (*see* Appendices V and VII)
      b. Antagonize sympathetic stimulation of renin secretion.
      c. Reduce cardiac output and heart rate.
   2. Beta "blockers" with ISA
      a. Intrinsic beta-1 agonist activity prevents direct cardiac effects.
      b. Noncardiac beta-2 stimulation leads to vasodilation.
      c. "Blockade" occurs mainly in response to stimuli.
   3. Beta-1 selective agents
      a. Have more effect on cardiac output and renin.
      b. Have less effect on peripheral resistance and bronchi.
   4. Beta-1-selective blockers with ISA
      a. Block beta-1 receptors at the heart and yet apparently have beta-2 agonist activity.

D. Diuretics
   1. Cause sodium loss.
   2. Cause some degree of vasodilation.
   3. Interestingly, calcium channel blockers also lead to net negative sodium balance.

E. Angiotensin-converting enzyme inhibitors
   1. Inhibit renin-mediated angiotensin II production.
   2. Have additional effects independent of the **systemic** renin-angiotensin axis, which are poorly understood but may include:
      a. Vasodilation dependent on increased levels of kinins because converting enzyme is also a kininase.[2]
      b. Vasodilation due to increase in certain prostaglandins.
   3. In patients with relatively low plasma renin levels, converting enzyme inhibition may work through the inhibition of **local** renin-angiotensin systems in vascular endothelium and possibly even the brain.[3,4]

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