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VOLUME 2

COMPREHENSIVE TEXTBOOK OF MEDICAL PHYSIOLOGY

WITH CLINICALLY INTEGRATED APPROACH

G K Pal

Co-authors
Pravati Pal
Nivedita Nanda

5th Edition



As per the Revised Competency-based Medical Education Curriculum (NMC)

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CHAPTER

55 Regulation of Blood Pressure

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Learning Objectives: *On completion of study of this chapter*

The student will be able to: (MUST KNOW)

1. Define systolic blood pressure (BP), diastolic BP, mean arterial pressure and pulse pressure and give their normal values and significance.
2. List the factors affecting BP.
3. Outline the physiological variations of BP.
4. Describe the mechanisms of regulation of BP.
5. Draw a schematic diagram of baroreceptor reflex.
6. Explain the role of baroreceptor reflex in regulation of BP.
7. Understand the importance of chemoreceptor reflex, Cushing reflex, Bainbridge reflex and other reflexes in regulation of BP.
8. Appreciate the importance of sympathetic vasoconstrictor tone in regulation of BP.
9. Define Marey's law and give its physiological basis.
10. List the vasodilators and vasoconstrictors.
11. Realize the importance of renin-angiotensin-aldosterone system in regulation of BP.
12. Elucidate the role of kidney in long-term regulation of BP.
13. Trace the pathway and say the significance of sympathetic vasodilator system.

The student may also be able to: (DESIRABLE TO KNOW)

1. Describe the role of vascular smooth muscle in the regulation of BP.
2. Explain the role of vascular endothelium in the regulation of BP.
3. Describe the role of medulla (vasomotor center and cardioinhibitory center) in the regulation of BP.

INTRODUCTION

Blood pressure (BP) is an important vital sign and its effective regulation is fundamental to ensure normal health.

Vascular Tone

Tone of the blood vessel plays a crucial role in the regulation of blood pressure. **Tone of vascular smooth muscle** depends on many neural and humoral factors.

1. Smooth muscles of blood vessel, like other smooth muscles normally exhibit tone, ***a state of prolonged partial contraction***.
2. BP is mostly influenced by the **tone of blood vessels**, especially ***of the resistance vessels*** (arterioles and small arteries).
3. Vascular tone **increases by vasoconstriction** that increases blood pressure and **deceases by vasodilation** that decreases blood pressure.
4. **Vasoconstrictor and vasodilator agents** alter blood pressure by altering the activity of vascular smooth muscle.
5. These chemicals affect vascular tone by mainly altering the **intracellular calcium concentration** in vascular smooth muscle.

Vascular Smooth Muscle

Cell membrane of vascular smooth muscles contains **K^+, Ca^{++} and Cl^- channels**. Concentration of intracellular Ca^{++} ions and the activity of myosin light-chain kinase (**MLCK**) influence the contraction of vascular smooth muscles. The vascular tone that occurs due to prolonged contraction of vascular smooth muscle depends mainly on **latch-bridge mechanism**, though other factors also contribute to it.

1. **Influx of calcium** into the muscle due to opening of **voltage-gated calcium channels** (VGCC) increases cytosolic calcium.
2. **Calcium activates myosin light-chain kinase** that phosphorylates myosin light chain, which in turn causes muscle contraction.
3. Increased cytoplasmic calcium also causes **opening of ryanodine receptor-mediated calcium channels** in the sarcoplasmic reticulum (**calcium-mediated calcium release**) that increases release of calcium from this organelle.
4. Cytosolic calcium concentration increases to a greater extent that opens up the **calcium-activated K^+ channels** on cell membrane and causes **K^+ efflux (Fig. 55.1)**.
5. These potassium channels are **BK channels** (Big K^+ channels) as *K^+ efflux occurs at a very high rate* through these channels. Calcium acts on β_1 **subunits of BK channels**.

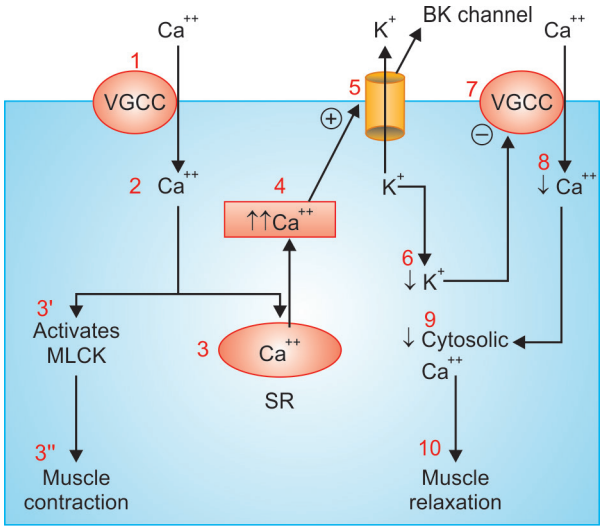


Fig. 55.1: Mechanisms of smooth muscle contraction and relaxation.

[VGCC: voltage-gated calcium channel; MLCK: myosin light-chain kinase; SR: sarcoplasmic reticulum; BK: big K^+ channel; +: stimulation; –: inhibition. Smooth muscle contraction and relaxation occur in 10 steps: **1.** Activation of VGCC; **2.** Influx of calcium that increases cytosolic calcium; **3.** Calcium-induced calcium release (calcium spark) from SR (also, increased cytosolic calcium activates MLCK that causes muscle contraction as in step 3′ and 3″); **4.** Maximal increase in cytosolic calcium; **5.** Very high cytosolic calcium activates BK channel; **6.** K+ efflux decreases cytosolic K^+; **7.** Change in membrane potential induced by K^+ efflux inhibits VGCC; **8.** Decreased calcium influx; **9.** Decreased concentration of cytosolic calcium; **10.** Muscle relaxation]

6. K^+ efflux increases the membrane potential that **closes the calcium channel** and produces relaxation.

PY5.11: Describe blood pressure, factors affecting blood pressure and its regulation.

PHYSIOLOGICAL ASPECTS

Definitions, Normal Values and Significance

Blood Pressure

Blood pressure is defined as the **lateral pressure exerted by the column of blood on the wall of arteries**.

1. Blood pressure means the **arterial pressure**.
2. The arterial pressure fluctuates during systole and diastole of the heart.

Systolic Blood Pressure

Definition

Systolic BP is defined as the **maximum pressure** recorded during the cardiac cycle. As maximum pressure is recorded during systole, the pressure is called systolic pressure.

Normal Value

Normal systolic BP is **100–119 mm Hg** in adults.

- Systolic BP, 120–139 mm Hg, is classified as **prehypertension** and 140 mm Hg or above is **hypertension**.

Significance

Systolic pressure **depends mainly on the cardiac output**. Thus, systolic pressure increases when cardiac output increases and decreases when cardiac output decreases.

1. However, systolic pressure is also affected by the **compliance of arteries**. When arteries become stiff as occurs in advanced age, systolic pressure increases.
2. In a stiff vessel, the *ability to accommodate a particular amount of cardiac output decreases* in comparison to a normal vessel.

Diastolic Blood Pressure

Definition

Diastolic blood pressure is defined as the **minimum pressure** recorded during the cardiac cycle. As the minimum pressure is recorded during diastole, the pressure is called diastolic pressure.

Normal Value

Normal diastolic BP is **60–79 mm Hg** in adults.

- Diastolic BP 80–89 mm Hg is classified as prehypertension and 90 mm Hg or above is hypertension.

Significance

Diastolic blood pressure *depends primarily on peripheral resistance*. Therefore, diastolic pressure changes with alteration in peripheral resistance.

1. Peripheral resistance depends mainly on the **diameter of the blood vessels** and **viscosity** of the blood.
2. **Vasoconstriction** increases diastolic pressure and **vasodilation** decreases diastolic pressure.

Pulse Pressure

Definition

Pulse pressure (PP) is the **difference between systolic and diastolic** blood pressure.

Normal Value: 20–50 mm Hg.

Significance

This is the pressure that maintains the **normal pulsatile nature** of blood flow in the vascular compartment. The pulsatile nature of flow is required for the **perfusion of the tissues**.

Mean Arterial Pressure

Definition

Mean arterial pressure (MAP) is the **average pressure** recorded during the cardiac cycle.

As the duration of systole is less than the duration of diastole, the MAP is less than the value halfway between systolic and diastolic pressures **(Fig. 55.2A)**.

It is calculated as:

MAP = Diastolic pressure + 1/3 PP

Normal value: 75–105 mm Hg.

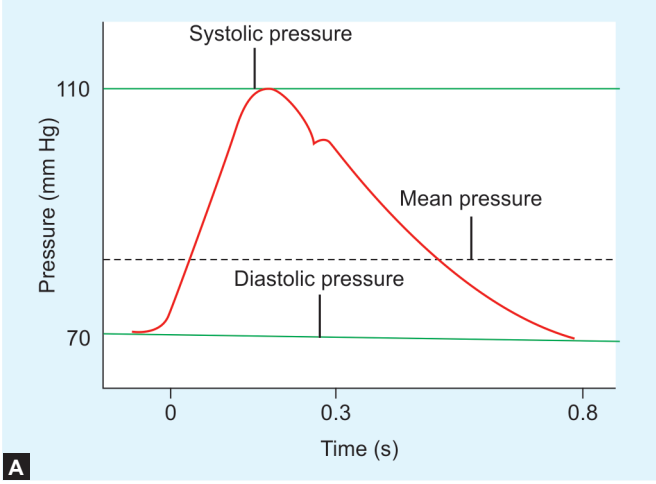
Significance

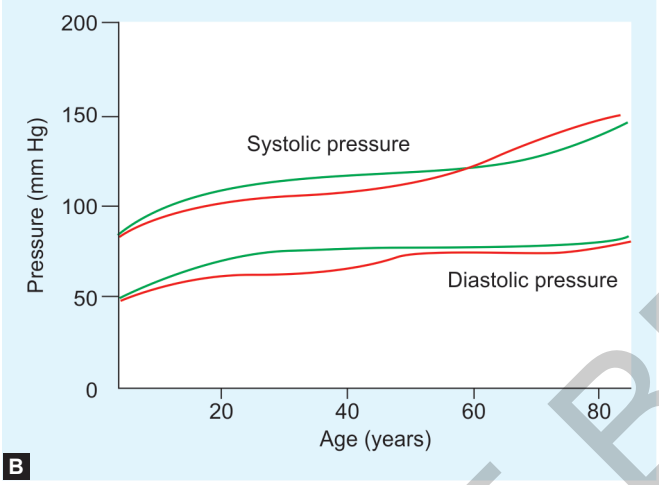
The MAP is the pressure that helps in **forward movement of blood** in the lumen of blood vessels. It also maintains **perfusion of tissues**.

Casual Blood Pressure

BP measured at **any time of the day** or night is known as the casual pressure. Casual BP is important as it reflects the actual BP of the individual irrespective of other influences.

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Figs. 55.2A and B: **(A)** Normal arterial pressure during a cardiac cycle. Note, the maximum pressure recorded is systolic pressure and the minimum pressure recorded is diastolic pressure. The mean arterial pressure is close toward the diastolic pressure as the duration of diastole is more than the duration of systole. **(B)** Effects of age and gender on BP. Note, during the reproductive age, the systolic and diastolic pressures are less in females (red line) than in males (green line). However, after menopause, in females, diastolic pressure becomes almost equal with males, and systolic pressure may even become more than in males.

Basal Blood Pressure

Blood pressure recorded **in the basal state** is called basal blood pressure. In clinical practice, basal blood pressure is recorded following *physical and mental rest for 10–20 minutes* in supine position **(resting basal BP)**.

Factors Affecting Blood Pressure

Blood pressure = **Cardiac output** × **peripheral resistance**

Therefore, factors that influence cardiac output or peripheral resistance affect the blood pressure. Alteration in **cardiac output mainly affects systolic pressure** and alteration in **peripheral resistance mainly affects diastolic pressure**.

Cardiac Output

As cardiac output is the product of stroke volume and heart rate, any factor that affects either of these two parameters, affects cardiac output. The **stroke volume** is affected by ***preload, afterload and myocardial contractility***, and the **heart rate** is mainly affected by ***autonomic influences*** (factors affecting cardiac output have been discussed in detail in Chapter 48).

Peripheral Resistance

Peripheral resistance depends on diameter of blood vessel and viscosity of blood (factors affecting peripheral resistance have been discussed in detail in Chapter 50).

Physiological Variations

Age

Blood pressure **increases with age.**

In children: Systolic pressure ranges from 90 to 120 mm Hg and diastolic pressure from 50 to 80 mm Hg.

In adults: Systolic pressure ranges from 100 to 119 mm Hg and diastolic pressure from 60 to 79 mm Hg. Systolic BP between 120 mm Hg and 139 mm Hg and diastolic BP between 80 and 89 mm Hg are classified as prehypertension.

In elderly: The upper limit of systolic pressure is considered to be 140 mm Hg. However, ***diastolic pressure above 90 mm Hg*** is always considered as hypertension.

Gender

Blood pressure is comparatively **less in females** during their reproductive life **(Fig. 55.2B)**.

- This difference disappears after menopause.
- Blood pressure is less in females due to the effect of progesterone that relaxes the smooth muscles of the blood vessels and estrogen that prevents atherosclerosis.

Eating

Blood pressure **increases after a meal**. This is due to increased body metabolism that increases circulation and cardiac output following food intake.

Sleep

Blood pressure is **less during sleep** than in the awakened state. When human being is awake, he is under the influence of stress and strain of life.

1. Acute stress activates sympathetic activity that increases blood pressure. The level of **stress and sympathetic tone are less** in sleep.
2. In addition, **absence of physical activity** during sleep aids to decrease in blood pressure.

Emotion and Excitement

In emotion and excitement, **increased sympathetic discharge** increases blood pressure.

Exercise

During exercise, the **systolic pressure always rises** due to increased cardiac output.

- **Diastolic pressure** depends on the degree of exercise, which increases in mild exercise due to vasoconstriction. In moderate exercise, DBP increases, remains unchanged or falls. In severe exercise, it usually decreases (but may remain unchanged or may exhibit mild increase) due to metabolic vasodilation and increased body temperature.
- Thus, **pulse pressure is more** in severe exercise.

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Posture

On **immediate standing** from supine posture, **blood pressure decreases** due to venous pooling of blood in the lower limbs.

1. However, blood pressure returns to normal or may mildly increase due to the immediate corrections initiated by baroreceptor reflex.
2. Baroreceptor reflex controls blood pressure in 15–30 seconds.

Temperature

Blood pressure **decreases in hot environment** due to *cutaneous vasodilation* and **increases in cold** environment due to *vasoconstriction*.

Pregnancy

Cardiac output **increases in pregnancy** due to ***increased blood volume*** that increases systolic pressure.

1. **Diastolic pressure falls** due to decreased peripheral resistance, which occurs due to the **effect of progesterone** on blood vessels. Progesterone relaxes smooth muscle and therefore causes **vasodilation**.
2. Thus, **pulse pressure increases** in pregnancy.

REGULATION OF BLOOD PRESSURE

The mechanisms involved in regulation of blood pressure can be divided broadly into **two categories**: (1) Short-term regulation and (2) long-term regulation.

1. **Short-term regulation** is mainly neural.
2. **Long-term regulation** is mainly hormonal and renal.

Scientist contributed



Carl Ludwig

Carl Friedrich Wilhelm Ludwig (1816–1895) was an outstanding German physiologist. For his contributions, at University of Leipzig, the Physiological Institute is designated as **Carl Ludwig Institute of Physiology**. He contributed enormously to cardiovascular physiology and BP regulation. He discovered vasomotor reflexes and proposed renal secretion theory for regulation of BP. For his outstanding contributions, the **Carl Ludwig Honorary Medal** is awarded by the German Society for Cardiology to outstanding investigators in the area of cardiovascular research.

Short-term Regulation of BP

Short-term regulation means the regulation of blood pressure **within seconds to minutes**, or in an hour. Short-term regulation occurs mainly by the **neural mechanisms**, though the ***vascular and hormonal mechanisms*** also contribute to it.

Mechanisms of short-term regulation of blood pressure are as follows:

1. **Neural mechanisms:**
   - ***Autonomic regulation***
     - Sympathetic control
     - Parasympathetic control
   - ***Medullary control***
   - ***Hypothalamic control***
   - ***Cortical control***
   - ***Reflex regulation:***
     - Baroreceptor reflex
     - Chemoreceptor reflex
     - Cushing reflex
     - Somatosympathetic reflex
     - Atrial stretch reflex
     - Ventricular and pulmonary stretch reflexes
     - Nonphysiological chemoreflexes (coronary and pulmonary chemoreflexes)
     - Bainbridge reflex
2. **Vascular mechanisms:**
   - Capillary fluid shift
   - Stress relaxation
3. **Hormonal mechanisms:**
   - Catecholamines
   - Renin–angiotensin system
   - Antidiuretic hormone (ADH)
   - Atrial natriuretic peptide (ANP)
   - Kinin–kallikrein system
   - Histamine
   - Endothelins
   - Endothelium-derived relaxing factor (EDRF)
   - Adrenomedullin.

Neural Mechanisms of BP Regulation

Autonomic Regulation

Autonomic control of blood pressure is **mainly by sympathetic control**, as systemic blood vessels are ***innervated by sympathetic fibers*** and they lack parasympathetic innervation.

Sympathetic Control

Sympathetic regulation is the **main control mechanism** for blood pressure regulation as the sympathetic fibers are the **final pathways** of all neural inputs to the blood vessels. There are **two types of sympathetic systems** for blood vessels:

1. Sympathetic vasoconstrictor system
2. Sympathetic vasodilator system

Sympathetic Vasoconstrictor System

Noradrenergic fibers supplying blood vessels are **vasoconstrictor in nature**. Therefore, stimulation of these fibers **increases blood pressure**.

1. Especially, the ***sympathetic innervation of resistance vessels*** like arterioles, small arteries and metarterioles is important for the regulation of blood pressure.
2. The sympathetic vasoconstrictor fibers **originate from** the ***intermediolateral horn of the spinal cord*** and innervate blood vessels, adrenal medulla, and heart **(Fig. 55.3)**.
3. Stimulation of these fibers ***produces vasoconstriction*** and therefore they are called vasoconstrictor fibers.
4. It is important to note that the sympathetic vasoconstrictor fibers have the **basal rate of tonic discharge**, which is essential for maintaining the normal **vascular tone**. Thus, the vascular sympathetic tone is also known as **sympathetic vasoconstrictor tone**.
5. Simultaneously, sympathetic stimulation also produces **venoconstriction**. Venoconstriction ***increases venous return*** and cardiac output and shifts blood from the venous

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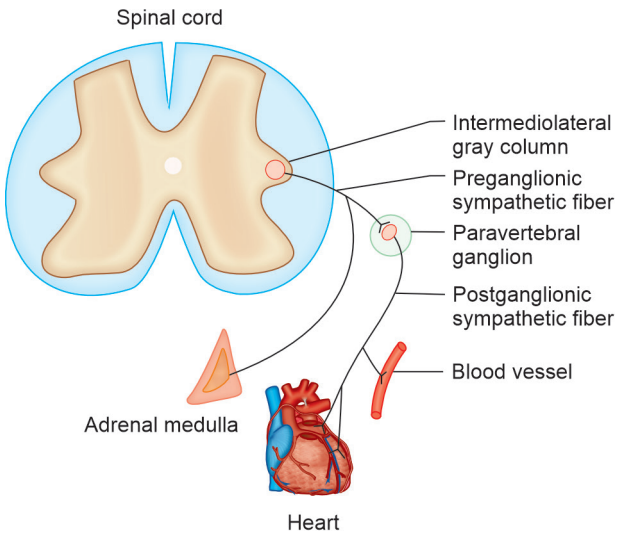


Fig. 55.3: Sympathetic vasoconstrictor system. These fibers originate from intermediolateral gray column of spinal cord. The postganglionic fibers innervate blood vessels and heart, and preganglionic fibers terminate in adrenal medulla.

compartment to the arterial compartment that aids in increasing blood pressure.

6. Sympathetic stimulation also increases blood pressure by its **cardiostimulatory effects** and **effects on catecholamine secretion** from adrenal medulla.

In summary, sympathetic stimulation increases BP by following mechanisms:

i. **Vasoconstriction**, especially constriction of resistance vessels
ii. **Venoconstriction** that increases venous return
iii. **Cardiac stimulation** (increased heart rate and myocardial contractility)
iv. Increased **secretion of catecholamines** from adrenal medulla.

Sympathetic regulation is the essential component of blood pressure regulation. **Decreased rate of tonic discharge** of sympathetic vasoconstrictor nerves produces **vasodilation** that results in fall in blood pressure. For example, hypotension following spinal transection occurs due to decreased sympathetic outflow (see below).

Sympathetic Vasodilator System

Stimulation of sympathetic fibers supplying **arteries and arterioles of skeletal muscles** produces vasodilation as they are innervated by ***sympathetic cholinergic fibers***. Therefore, this system of sympathetic innervation of blood vessel is called as sympathetic vasodilator system.

1. These fibers **originate from frontal cortex** and relay in **hypothalamus and midbrain (Fig. 55.4).**
2. Fibers ***pass through medulla without relay*** in medullary cardiovascular centers and ***terminate in intermediolateral gray column*** of spinal cord.
3. It is to be noted that there is **no basal tonic discharge** of sympathetic vasodilator fibers.

Parasympathetic Control

Systemic blood vessels are not supplied by parasympathetic fibers. However, vagal stimulation *decreases blood pressure* **by decreasing heart rate and cardiac output**.

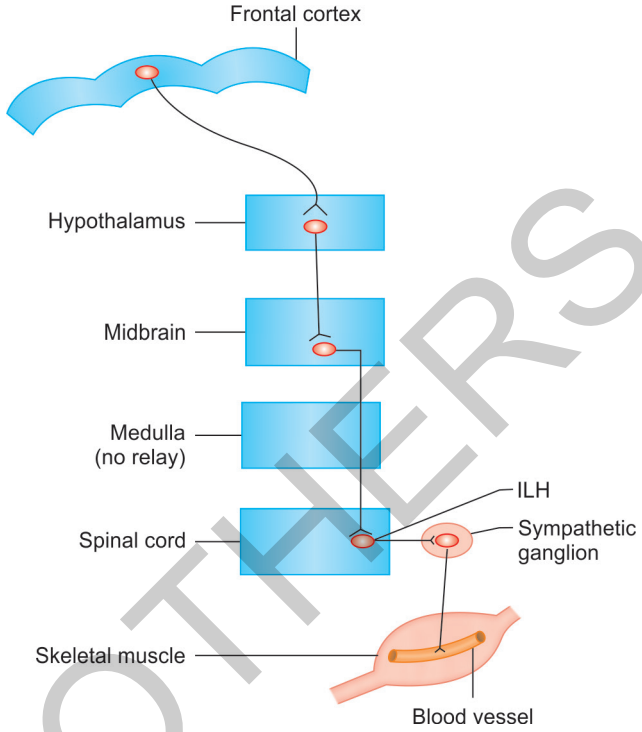


Fig. 55.4: Sympathetic vasodilator system. Fibers originating from frontal cortex relay in hypothalamus and midbrain. From midbrain, fibers descend down to intermediolateral horn (ILH) of spinal cord without contacting neurons in the medullary cardiorespiratory centers. From ILH, sympathetic fibers terminate on blood vessel of skeletal muscle.

Medullary Control

Cardiovascular centers are mainly located in the medulla. **Medullary cardiovascular centers** are broadly divided into two: (1) **vasomotor center and (2) cardioinhibitory center**.

Vasomotor Center

This is also called **vasomotor area**. It is present in the ***medulla***.

1. This area has caudal, intermediate, and rostral parts; and accordingly they are called caudal ventrolateral medulla (CVLM), intermediate ventrolateral medulla (IVLM), and rostral ventrolateral medulla (RVLM).
2. Though **RVLM is the major area** in this group of neurons, these three neuronal groups are collectively known as **vasomotor centers** (VMCs).
3. CVLM receives excitatory inputs from nucleus tractus solitarius (NTS), which in turn projects to the RVLM. **Projection of CVLM to RVLM is inhibitory** (GABA is the neurotransmitter). Thus, NTS inhibits RVLM. The RVLM directly projects to the intermediolateral gray column of the spinal cord (via **bulbospinal pathway**) from where the sympathetic vasoconstrictor fibers originate **(Fig. 55.5)**.
4. Neurons in VMC (RVLM) are *always active* and provide **tonic excitatory drive** to the spinal cord neurons. The **basal tonic sympathetic vasoconstrictor tone** is due to the drive of preganglionic sympathetic neurons by the **tonic discharge of VMC neurons**.
5. This **medullary-spinal cord-cardiovascular axis** is the most important pathway for control of blood pressure. As vasomotor center regulates activity of this pathway, control of blood pressure by it is called **vasomotor control**.

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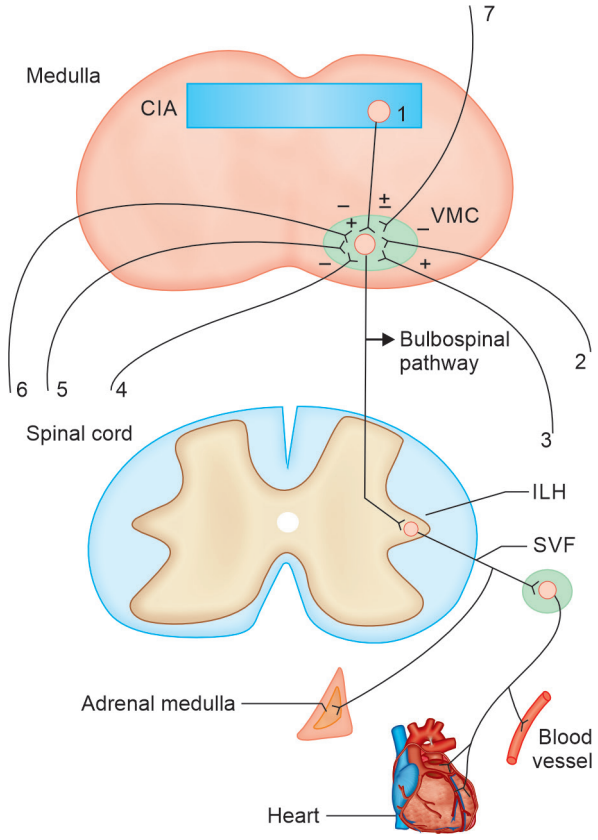


Fig. 55.5: Vasomotor control. Vasomotor center (VMC) in the medulla is the primary center in the brain from where sympathetic vasoconstrictor fibers (SVF) receive excitatory drive. Fibers from VMC descend down in the bulbospinal pathway to terminate on the cell bodies in the intermediolateral horn (ILH) of spinal cord and stimulate the vasoconstrictor fibers. VMC receives inhibitory input from cardioinhibitory area (CIA) in the medulla via interneurons (1). VMC also receives inhibitory input from aortic and carotid baroreceptors (2), excitatory input from aortic and carotid chemoreceptors (3), inhibitory input from lungs (4), excitatory input from ascending pain pathways (5), excitatory proprioceptive input (6), and from limbic system (7).

6. **Stimulation of VMC** causes intense vasoconstriction and cardioacceleration that ***increases blood pressure*** **(Clinical Box 55.1)**.
7. **Inhibition of VMC** causes vasodilation and cardioinhibition that ***decreases blood pressure***.
8. Influence of VMC on control of blood pressure is so crucial that **loss of this influence** as occurs following transection of spinal cord results in **gross hypotension** in the acute phase of spinal shock.

Vasomotor center **receives inputs** from following structure of the body **(Fig. 55.5)**:

i. Aortic and carotid baroreceptors (inhibitory)
ii. Cardiopulmonary baroreceptors (inhibitory)
iii. Carotid and aortic chemoreceptors (excitatory)
iv. Ascending pain pathways (excitatory)
v. Ascending pathways carrying proprioceptive information (excitatory)
vi. Lungs via vagus nerves (inhibitory)
vii. Limbic cortex via hypothalamus (usually excitatory, but may be inhibitory).

Following are the **effects of activation of these inputs**:

1. **Excitatory inputs that increase BP:** Cortex via hypothalamus, mesencephalic periaqueductal gray, brainstem reticular formation, pain pathways, somatic afferents (somatosympathetic reflex), carotid and aortic chemoreceptors.
2. **Inhibitory inputs that decrease BP:** Cortex vis hypothalamus, NTS via CVLM, caudal medullary raphe nuclei, lung inflation afferents, carotid, aortic and cardiopulmonary baroreceptors.
3. **Direct stimulation:** Hypoxia and carbon dioxide.

Scientist contributed

Ludwig Traube (1818–1876) demonstrated variations in activity of vasomotor center in the medulla oblongata. He described the fluctuation in BP synchronized with respiration, and the waveforms are popularly known as **Traube–Hering waves**.



Ludwig Traube

Clinical Box 55.1

Neurovascular compression of RVLM causes essential hypertension: It has been reported that neurovascular compression of RVLM (VMC) causes essential hypertension in some individuals by increasing sympathetic activity. It has also been reported that ***surgical decompression of RVLM*** could relieve hypertension in some hypertensive patients.

Cardioinhibitory Centers

Cardioinhibitory center in the medulla is formed by **nucleus tractus solitarius** (NTS), **nucleus ambiguous**, and **dorsal motor nucleus of vagus**. Stimulation of these areas results in **bradycardia and decreased cardiac output** by two mechanisms.

1. Vagus nerve originates from cardioinhibitory areas, mainly from NTS, which on stimulation ***activates vagal output*** that inhibits heart functions **(Fig. 55.6)**.
2. Nucleus tractus solitarius inhibits RVLM (vasomotor center) via local inhibitory interneurons that in turn ***decreases sympathetic output***.

Thus, **stimulation of NTS** *increases vagal activity and decreases sympathetic activity* that in turn results in bradycardia, decreased cardiac output, vasodilation, and **decreased blood pressure.**

Hypothalamic Control

Stimulation of **anterior hypothalamus** produces hypotension and bradycardia, and stimulation of **posterolateral part of hypothalamus** produces hypertension and tachycardia.

1. Hypothalamus controls **cutaneous blood flow** that affects blood pressure.
2. Hypothalamus also mediates the effects of cardiovascular reflexes such as **atrial stretch reflex**.
3. A **reciprocal connection** exists between *hypothalamus and vasomotor center*.
4. ***Limbic cortex*** influences vasomotor center via hypothalamus.
5. Hypothalamus also **secretes ADH** that conserves body water in hypovolemia and hypotension, a mechanism involved in long-term regulation of blood pressure.

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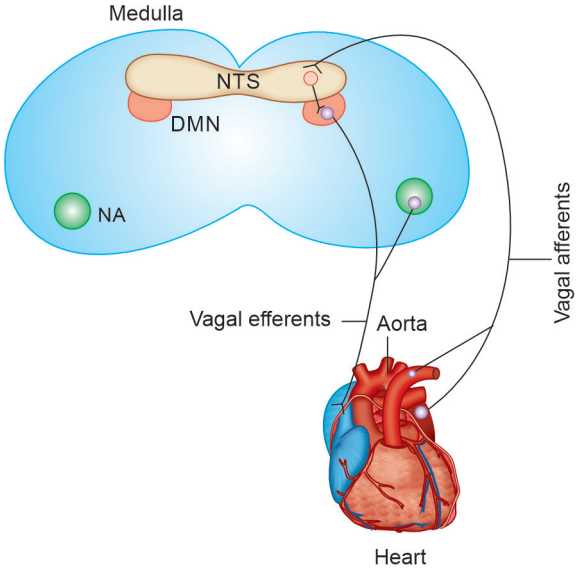


Fig. 55.6: Cardioinhibitory centers (CIC) in the medulla. These are mainly three vagal nuclei. Nucleus tractus solitarius (NTS) is the major one. The others are dorsal motor nucleus (DMN) of vagus and nucleus ambiguous (NA). 10th cranial nerve carries sensation from heart and aorta to the CIC. Also, fibers project to heart via vagal efferent fibers. NTS is the major receiving nucleus and DMN is the major efferent nucleus. NTS projects to DMN.

Cortical Control

Cortex does not directly influence blood pressure.

1. However, stimulation of **motor and premotor cortices** usually *increases blood pressure*.
2. **Sympathetic vasodilator system** originates from frontal cortex.

Reflex Regulation of Blood Pressure

Regulation of blood pressure by various cardiovascular reflexes is the most important short-term mechanism as reflexes operate swiftly and effectively in response to change in blood pressure. The important reflexes are baroreceptor reflex, chemoreceptor reflex, and Cushing reflex (the list of other reflexes is given above).

Baroreceptor Reflex

Among all the cardiovascular reflexes, most important is the baroreceptor reflex as it **regulates blood pressure within seconds**. Baroreceptor reflex is therefore a life-saving reflex. This is also called baroreflex or **Sinoaortic Reflex**.

Receptors and Stimulus

The receptors for baroreceptor reflex are **baroreceptors**. They detect change in pressure in the blood vessels and chambers of the heart. Usually, baroreceptors are classified into two categories: High-pressure and low-pressure receptors. ***High-pressure baroreceptors*** are located in the ventricle and arterial side of circulation, and the ***low-pressure baroreceptors*** are mainly present in the atria and pulmonary circulation (cardiopulmonary baroreceptors).

1. Receptors for baroreceptor reflex are **high-pressure baroreceptors** that are present in the wall of the **carotid sinus and aortic arch.**

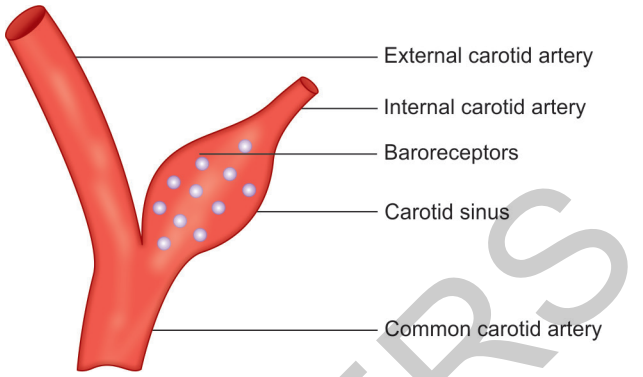


Fig. 55.7: Location of the carotid sinus. Note, it is the initial dilated portion of the internal carotid artery at its bifurcation from common carotid artery and baroreceptors are located in the wall of the carotid sinus.

2. **Carotid sinus** is the initial dilated portion of the internal carotid artery at its origin from common carotid artery **(Fig. 55.7)**.
3. These receptors are ***branched, knobby, and intertwined*** terminals of myelinated nerve fibers.
4. Baroreceptors ***detect change in pressure*** in blood vessels in the wall of which they are located.
5. The **increase in blood pressure** causes distension of carotid sinus and aortic arch, and ***stimulates receptors*** as they respond to stretch of the organ.
6. Conversely, **decreased pressure** *decreases receptor stimulation*.

Afferent Pathways

Ninth cranial nerve (glossopharyngeal nerve) is the afferent from carotid sinus, and **10th cranial nerve** (vagus nerve) is the afferent from aortic arch **(Fig. 55.8)**.

1. The **fibers from carotid sinus in the glossopharyngeal nerve** form a distinct branch called carotid sinus nerve. This is also called as buffer nerve as it buffers blood pressure when blood pressure changes.
2. The **fibers in the vagus nerve** that carry sensation from aortic arch form the aortic nerve. However, aortic nerve forms a *distinct branch* of vagus nerve *only in rabbit*.
3. **Distension** of carotid sinus and aortic arch causes **stretching of baroreceptors** and *increases firing* (nerve traffic) in **9th and 10th cranial nerves,** respectively.

Centers

Centers for baroreceptor reflex are **medullary cardiovascular centers**. These include *vasomotor center* and *cardioinhibitory center* (as described above in "Medullary Control").

Vasomotor center: The vasomotor center (VMC) is the ***central sympathetic center***, as through ***bulbospinal pathway*** VMC projects to the intermediolateral gray column of the spinal cord from where *sympathetic fibers originate.*

Cardioinhibitory center: Nucleus tractus solitarius (NTS) is the major cardioinhibitory center. This is the ***main parasympathetic center*** as *vagus nerve originates* from NTS.

Normally, ***NTS inhibits vasomotor center*** via interneurons.

Thus, excitation of cardioinhibitory center **stimulates vagus nerve** and via inhibition of VMC **inhibits sympathetic fibers**.

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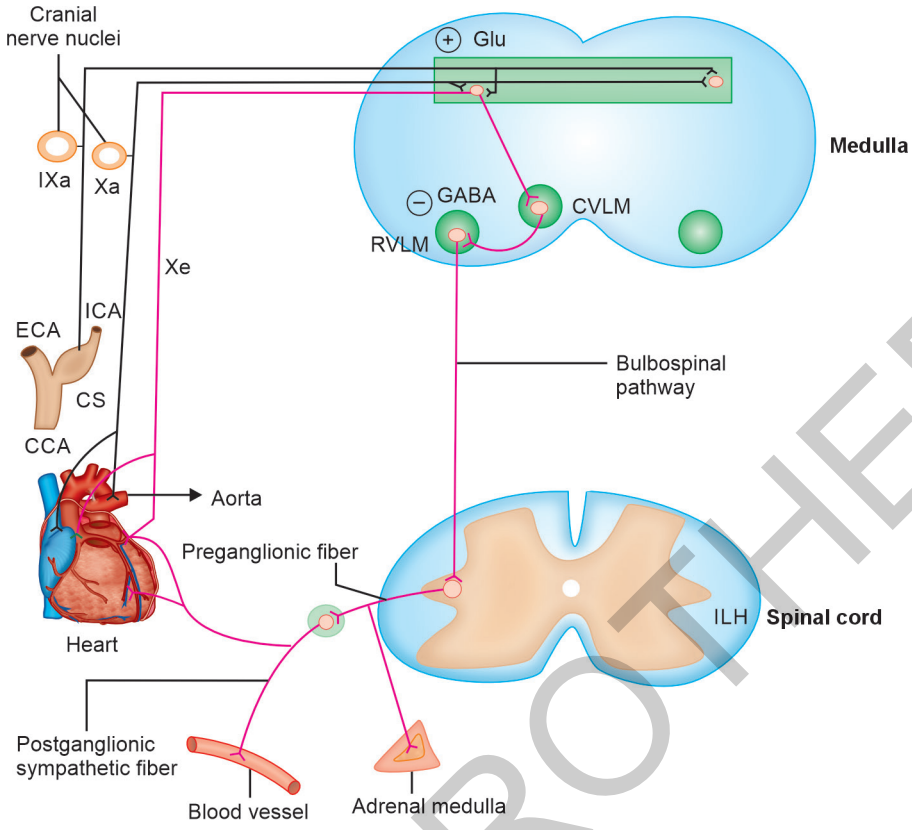


Fig. 55.8: Baroreceptor reflex. Afferent pathway is formed by 9th (IXa) and 10th cranial nerves (Xa), and efferent pathway is formed by efferent fibers of 10th cranial nerve (Xe), and sympathetic vasoconstrictor system that originates from VMC. (Note: The nuclei and fibers of only one half of medulla and spinal cord are shown in the figure)

(CCA: common carotid artery; ICA: internal carotid artery; ECA: external carotid artery; CS: carotid sinus; NTS: nucleus tractus solitarius; VMC: vasomotor center; RVLM: Rostral ventrolateral medulla; CVLM: Caudal ventrolateral medulla; +: excitatory neurotransmitter glutamate (Glu); –: inhibitory neurotransmitter GABA; ILH: intermediolateral horn)

Efferent Pathways and Effector Organs

Efferent fibers for baroreceptors are *sympathetic fibers and vagus nerve*.

1. **Sympathetic fibers** originate from *intermediolateral gray column of the spinal cord*, which is controlled by vasomotor center.
2. **Vagus nerve** originates from NTS.
3. Vagus nerve innervates **heart** and sympathetic fibers innervate **heart and blood vessels**.

Responses

Responses depend on the nature of change (increase or decrease) in blood pressure. Responses also depend on degree and rate of change in blood pressure.

When blood pressure increases: Increase in blood pressure ***stimulates baroreceptors*** in carotid sinus and aortic arch that ***increases the nerve traffic*** in 9th and 10th cranial nerves.

1. This leads to the **excitation of the NTS** in the medulla, which in turn **inhibits vasomotor center** (RVLM) via interneurons.
2. Inhibition of VMC ***decreases sympathetic output*** and causes *vasodilation, bradycardia, decrease in cardiac output* and **fall in blood pressure.**
3. Excitation of NTS also directly inhibits heart by ***stimulating vagus nerve*** **(Fig. 55.9)**.

When blood pressure decreases: Fall in blood pressure causes ***less distension*** of carotid sinus and aortic arch that decreases

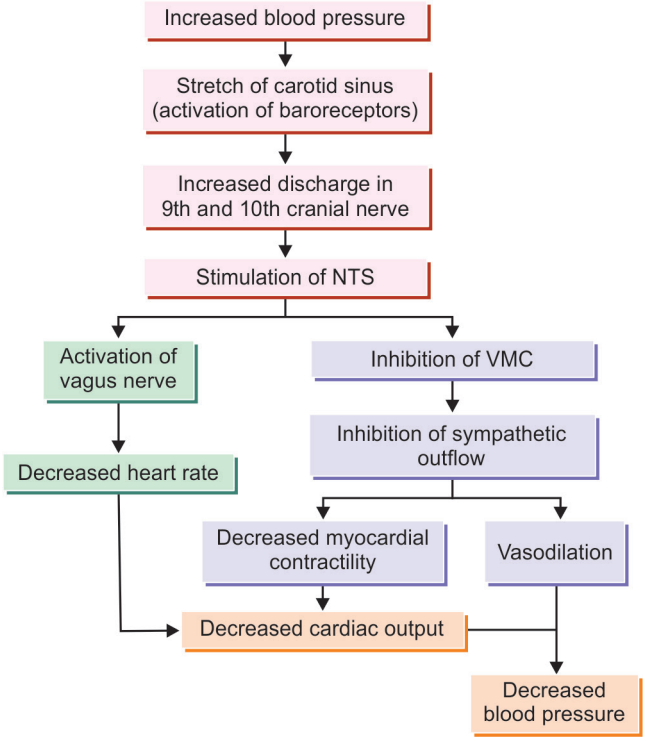


Fig. 55.9: Cardiovascular responses activated by increased blood pressure.

(NTS: nucleus tractus solitarius; VMC: vasomotor center)

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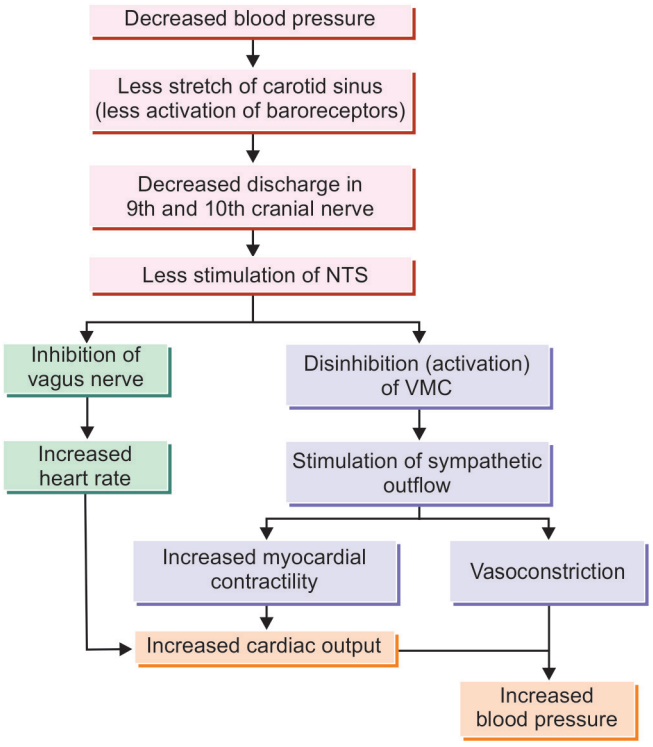


Fig. 55.10: Cardiovascular responses activated by decreased blood pressure.

(NTS: nucleus tractus solitarius; VMC: vasomotor center)

receptor activity and **inhibits discharge rate** in the afferent nerves.

1. This **inhibits NTS** that in turn causes **disinhibition** of VMC (removal of inhibition of VMC).
2. Thus, VMC (RVLM) is stimulated that ***increases sympathetic discharge*** and causes *vasoconstriction, tachycardia, increased cardiac output,* and **increase in blood pressure.**
3. Inhibition of NTS also stimulates heart by ***inhibiting vagus nerve*** **(Fig. 55.10)**.
4. Sympathetic activation also promotes ***release of catecholamines*** from adrenal medulla that stimulates heart and cause vasoconstriction.

Pressure Range for Baroreflex Regulation

Baroreceptors regulate blood pressure in the pressure range of **50–200 mm Hg**.

1. However, a **linear relationship** is observed for the change in blood pressure and the baroreceptor discharge between pressure range of **70 and 140 mm Hg**.
2. No response is detected when pressure is less than 50 mm Hg and no further increase in response occurs when pressure is more than 200 mm Hg **(Fig. 55.11)**.

Types of Responses

Baroreceptors respond to change in **pulse pressure** and change in **mean arterial pressure**. Accordingly, there are ***two types*** of responses: Dynamic response and static response.

1. Response to change in pulse pressure is called **phasic or dynamic response** and response to change in sustained pressure (mean pressure) is called **tonic or static response**.

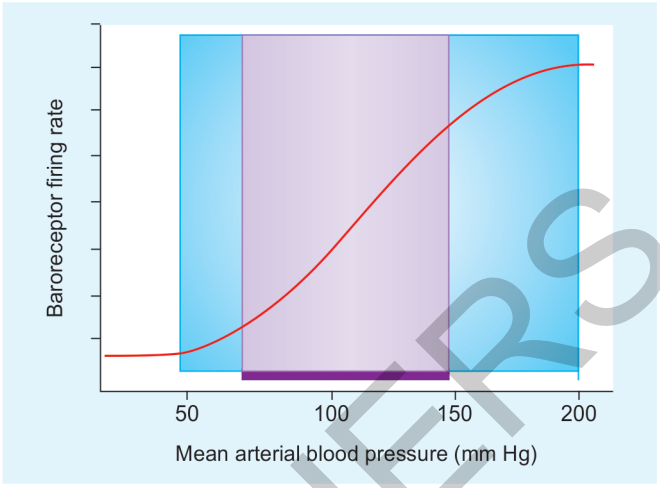


Fig. 55.11: Pressure range of baroreceptor reflex. Note, baroreceptor responds to pressure change between 50 and 200 mm Hg. However, maximum baroreceptor discharge occurs between 70 and 140 mm Hg as indicated by the dark bar below the pressure curve. There is no baroreceptor activation before 50 mm Hg and after 200 mm Hg.

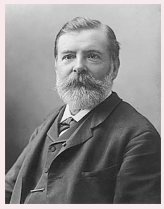
2. Decrease in pulse pressure without change in mean arterial pressure decreases carotid sinus discharge, and decrease in mean arterial pressure without change in pulse pressure also decreases sinus nerve discharge.
3. However, changes in pulse pressure and mean arterial pressure usually occur simultaneously.

Physiological Significance of Baroreceptor Reflex

1. When blood pressure falls, baroreceptor reflex **operates within few seconds** to correct the pressure, which is essential and life-saving in acute hypotension and hemorrhage. This is also **life-saving in day-to-day activities (Application Box 55.1)**. For example, blood pressure falls by about 30% on standing from lying posture, which is immediately corrected by baroreceptor reflex. Thus, baroreceptor reflex is the **first and foremost reflex** for regulation of blood pressure.
2. Baroreceptor reflex regulates blood pressure when pressure change is within the **range of 50–200 mm Hg**. Thus, baroreceptors and their reflex pathway constitute a feedback mechanism to stabilize blood pressure ***over a wide range of fluctuation*** in pressure.
3. Baroreceptor reflex explains the physiological basis for **Marey's Law**, which states that *heart rate is inversely proportional to blood pressure* (but not the vice versa).
4. Baroreceptor resetting occurs in chronic hypertension (discussed below).

Scientist contributed

Etienne Jules Marey (1830–1904), French physiologist invented sphygmograph and demonstrated the inverse relation between blood pressure and heart rate, which is popularly known as **Marey's Law**. He studied the details of blood circulation.



EJ Marey

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Application Box 55.1

Baroreflex is life-saving in daily life: Change in posture, especially getting up from supine posture decreases blood pressure due to peripheral pooling of blood that decreases effective blood volume, which may be equivalent to about 15% acute hemorrhage. Such an acute hemorrhage usually leads to shock. However, baroreflex adjusts BP so efficiently and promptly that we never realize we had a situation akin to acute severe hemorrhage.

Chemoreceptor Reflex

Receptors, Stimuli and Afferents: Receptors are ***chemoreceptors*** that are located in the **carotid bodies and aortic bodies**.

1. They respond to change in ***chemical composition of blood*** that occurs in conditions, such as hypoxia, hypercapnia, and acidosis.
2. **Afferents** from carotid body is ***9th cranial nerve*** and from aortic body is ***10th cranial nerve***.

Centers: Afferent fibers project to the medullary ***respiratory centers***. They also project to the cardiovascular centers, especially to both the **vasomotor and cardioinhibitory centers (Fig. 55.12)**.

Effects: Stimulation of chemoreceptors has **two phase effects**: (1) The primary effects and (2) the secondary effects.

1. The **primary effects** of chemoreceptor stimulation are ***bradycardia and vasoconstriction***. Stimulation of cardioinhibitory center causes bradycardia and stimulation of vasomotor center causes vasoconstriction.
2. However, hypoxia that stimulates chemoreceptors also causes pulmonary hyperventilation and increases catecholamine secretion from adrenal medulla that in turn increases heart rate (**secondary effects**).
3. Therefore, the **net effect** of stimulation of chemoreceptors is no change in heart rate or **mild tachycardia and vasoconstriction** that increases blood pressure.

BP Range: The **range of regulation** of blood pressure by chemoreceptor reflex is **40–70 mm Hg**.

CNS Ischemic Response (Cushing Reflex)

In conditions of **gross hypotension** as seen in acute severe hemorrhage, blood flow is compromised to the vital organs of the body. ***Decreased cerebral blood flow*** produces hypoxia and hypercapnia of VMC.

1. Direct hypoxia and hypercapnia stimulate VMC to its maximum, which causes ***intense vasoconstriction*** so that raised pressure maintains minimum blood flow to important organs. The reflex response is called as **CNS ischemic response**.
2. This is activated when *blood pressure falls below 40 mm Hg*.
3. This is the **last physiological reflex to correct blood pressure**, failure of which leads to irreversible shock.

Effects of Raised ICP: When intracranial pressure (ICP) is high, as occurs in **brain tumor**, the blood flow to the vasomotor center decreases due to compression of cerebral blood vessels. This causes hypoxic stimulation of vasomotor center and causes intense vasoconstriction that in turn *increases blood pressure*. This is known as **Cushing reflex (Flowchart 55.1)**. The increase in blood pressure in carotid sinus *activates baroreceptor reflex* and causes **reflex bradycardia (Case 55.1)**. Therefore, bradycardia occurs in brain tumors **(Clinical Box 55.2)**.

Clinical Box 55.2

Bradycardia is a feature of brain tumors: Increased ICP causes reflex bradycardia by activation of Cushing and baroreceptor reflexes. Therefore, *bradycardia is a prominent feature of brain tumors* that increase intracranial pressure.

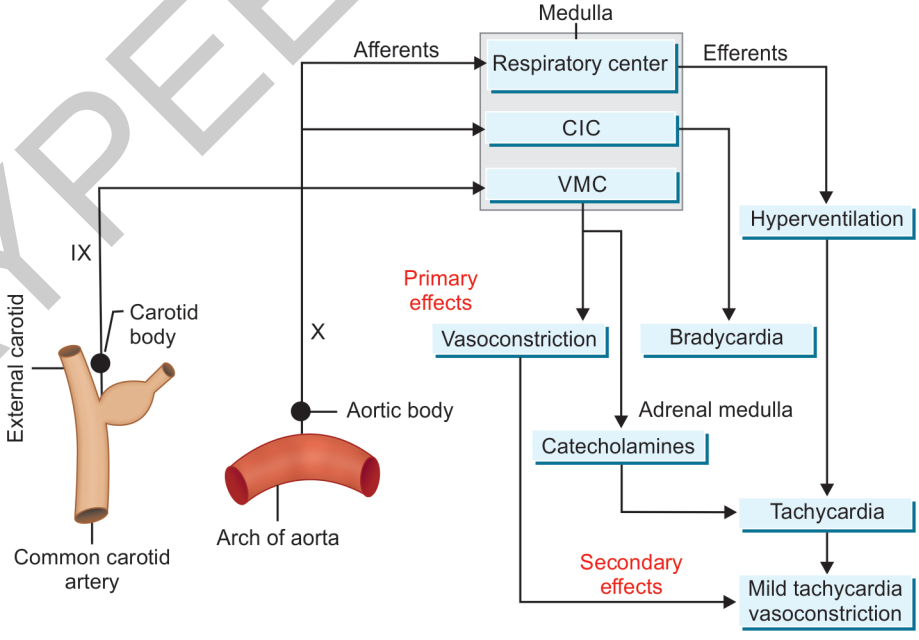
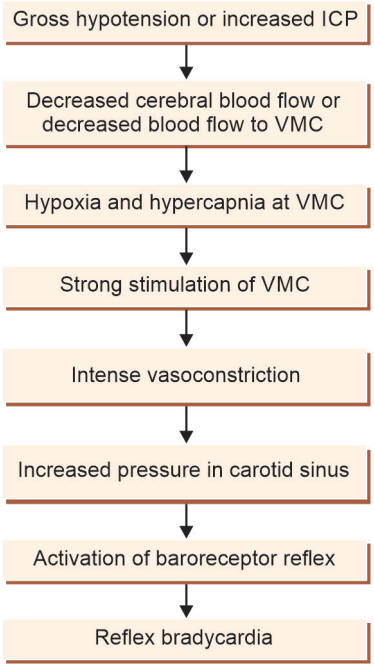


Fig. 55.12: Chemoreceptor reflex. Afferents from carotid and aortic bodies in 9th and 10th cranial nerve respectively stimulate cardioinhibitory center (CIC) to produce bradycardia, and vasomotor center (VMC) to produce vasoconstriction. These are primary effects. However, hyperventilation produced by stimulation of respiratory center and catecholamine secretion by stimulation of adrenal medulla result in tachycardia. Thus, net secondary effects are mild tachycardia and vasoconstriction.

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Flowchart 55.1: Cushing reflex (CNS ischemic response).



Scientist contributed



HW Cushing

Harvey William Cushing (1869–1939), an American neurosurgeon, developed neurosurgery as a branch of medicine, and he is often called as the "*Father of modern neurosurgery*". He had first observed the **Cushing reflex** which he described as the relationship between blood pressure and intracranial pressure. He had also described the cortisol excess is due to increased pituitary activity, which was later named after him as **Cushing's disease**.

Case 55.1: Early Clinical Exposure

A patient presented to medical emergency unit of the hospital with vomiting and headache for last one week following a moderate head injury, which has deteriorated today with blurred vision. O/E, he had bradycardia (HR 46 beats/min), systolic hypertension, and papilledema (swelling of optic disc).

Questions

1. What is your provisional diagnosis?
2. What is the likely reflex associated with it, and what is its physiological basis?
3. What is the possible "Triad" associated with it?
4. How will you confirm your diagnosis and how will you manage the case?

Answers

1. **Expanding brain lesion** that has increased intracranial pressure (ICP). Can be seen in traumatic brain injury (TBI) including hematomas and cerebral edema, and expanding brain tumor
2. **Cushing reflex:** The Cushing reflex (or **Cushing response**) is a physiological response to increased ICP. It is a life-saving, homeostatic mechanism by which the body attempts to maintain cerebral perfusion pressure (CPP) and blood flow in response to brainstem ischemia.
3. **Cushing triad:** This is seen in late stage of increased ICP, which manifests as (i) bradycardia (reflex bradycardia as described in preceding paragraph), (ii) increased SBP, and (iii) irregular respiration (due to compression of brain stem).
4. **Brain MRI:** It needs emergency treatment with immediate steps that include elevating the head of the bed (30°), sedation/analgesia, osmotherapy (mannitol or hypertonic saline), and hyperventilation, aimed at reducing cerebral metabolic demand, improving venous drainage, and reducing cerebral edema. Then the treatment should be done for the primary cause of increased ICP.

Somatosympathetic Reflex

The increase in blood pressure in response to **stimulation of somatic afferent nerves** is called somatosympathetic reflex.

1. It is activated usually following stimulation of **ascending pain fibers**.
2. Stimulation of proprioceptive pathway also increases blood pressure.
3. The pressor response is mediated via **vasomotor center** that receives excitatory input from ascending sensory pathway in the brain-stem **(Fig. 55.13)**.

Atrial Stretch Reflex

Two types of stretch receptors are present in atria: Type A and type B receptors.

1. **Type A receptors** are stimulated during atrial systole and **type B receptors** during peak atrial filling.
2. **Increased venous return,** as occurs in fluid retention or increased blood volume, ***increases atrial filling*** that stimulates **type B receptors**.
3. The **responses** to increased atrial filling are **vasodilation, decrease in blood pressure** and **tachycardia (Flowchart 55.2)**.
4. Conversely, decreased ECF volume decreases the activity of atrial stretch receptors that **increase ADH release**. ADH in turn causes water retention and increases blood volume and pressure.
5. Decreased atrial stretch also **stimulates sympathetic system** that increases renin release, which ***activates renin-angiotensin-aldosterone system*** (see below).

Cardiopulmonary Stretch Reflexes

Cardiopulmonary baroreceptors are distributed in the atria (discussed above), ventricles, and pulmonary vascular bed.

Ventricular Stretch Reflex

Increased distention of ventricle due to **excess ventricular filling** as occurs in increased blood volume (*volume overload*) results in **bradycardia, vasodilation, and hypotension**.

1. Thus, rise in blood pressure is checked.
2. Ventricular stretch reflex also plays a role **in maintaining vagal tone** that checks basal heart rate.

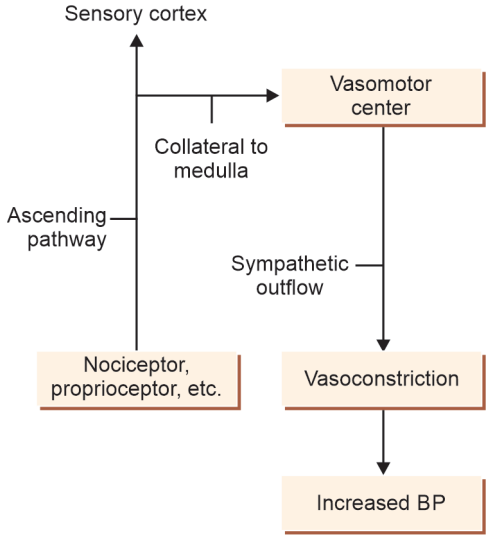
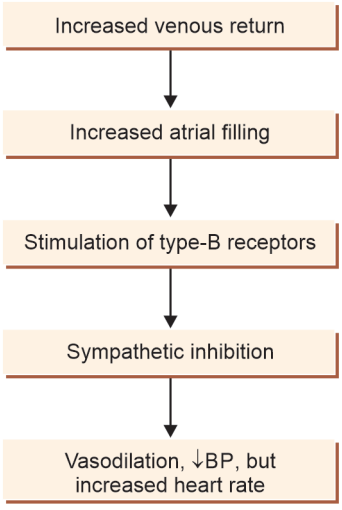


Fig. 55.13: Somatosympathetic reflex.

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Flowchart 55.2: Atrial stretch reflex.



Pulmonary Stretch Reflex

Pulmonary baroreceptors are located in ***pulmonary arteries***.

1. They are stimulated when ***pulmonary arterial pressure is increased,*** as occurs in pulmonary hypertension.
2. The responses observed are **bradycardia and hypotension.**

Nonphysiological Chemoreflexes

Coronary Chemoreflex

Chemoreceptors present in coronary arteries and ventricles are C-fiber endings.

1. The **afferents** from these chemoreceptors are ***vagal fibers***.
2. Injection of **chemicals**, such as *capsaicin, veratridinephenyl biguanide, and serotonin* into left coronary artery produces hyperventilation, **bradycardia, and hypotension**.
3. This is called coronary chemoreflex or **Bezold–Jarisch reflex.**
4. **In myocardial infarction**, chemical substances released from the infracted tissue stimulate ventricular chemoreceptors and produce bradycardia and hypotension (**Clinical Box 55.3**).

Pulmonary Chemoreflex

Injection of above-mentioned chemical substances into pulmonary arteries produce similar features (hyperventilation, **bradycardia, and hypotension)**.

1. The responses are **blocked by vagotomy**.
2. Such responses are observed in ***pulmonary embolism*** that produces pulmonary microinfarction.

Activation of cardiopulmonary chemoreceptors may also be the **part of defense mechanisms** protecting individuals from toxic chemical hazards. This may help **reducing entry of inspired toxic pollutants into the blood** and promoting their elimination.

Clinical Box 55.3

Vasovagal syncope is also attributed to Bezold–Jarisch reflex: Bradycardia with hypotension (vasovagal syncope) is also attributed to the activation of Bezold–Jarisch reflex (BJR). After prolonged standing, postural syncope occurs due to pooling of blood in lower extremities. Arterial hypotension sensed by baroreceptors initiates autonomic signals that increase heart rate and myocardial contractility. However, pressure receptors in the left ventricular wall sense low ventricular volume (less venous return) and activate BJR that results in paradoxical bradycardia and vasodilation, leading to sudden hypotension.

Bainbridge Reflex

Infusion of saline or transfusion of blood produces tachycardia, **if the initial heart rate is low**. This is called Bainbridge reflex (described by Bainbridge in 1915).

1. The receptors are **tachycardia producing atrial receptors** (TPAR) located in the atrial wall where vena cavas open into atria (at venoatrial junction).
2. The reflex is **abolished following vagotomy** as the responses are mediated by vagus nerves **(Flowchart 55.3)**.
3. The tachycardia produced by this reflex competes with the bradycardia produced by baroreceptor reflex in response to volume expansion.

Scientist contributed

Francis Arthur Bainbridge (1874–1921), British physiologist in 1915 demonstrated acceleration of the heart rate resulting from increased blood pressure, or increased distension of the large systemic veins and the right chamber of the heart. This reflex was named after him as Bainbridge reflex.



FA Bainbridge

Vascular Mechanisms

The vascular mechanisms **operate within seconds to minutes** of alteration in blood pressure. These are ***capillary fluid shift*** and ***stress relaxation***.

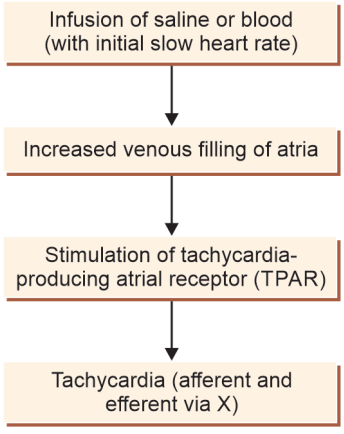
Capillary Fluid Shift

When blood pressure decreases rapidly as in acute hemorrhagic shock, the **hydrostatic pressure** in the capillaries **decreases**.

1. This causes ***shift of fluid*** from interstitial tissue space (extravascular compartment) into the intravascular compartment through the capillary membrane. This is called capillary fluid shift.
2. In this mechanism, about **300 mL of interstitial fluid** is added to the blood.
3. As a result, circulating **blood volume increases** and blood pressure returns to normal.

Reverse Capillary Shift: Reverse mechanism operates when **sudden rise in blood pressure** increases capillary pressure and

Flowchart 55.3: Bainbridge reflex.



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facilitates capillary filtration. This *decreases blood volume* and tends to lower blood pressure.

Stress Relaxation

When blood pressure **increases abruptly**, blood vessels **distend** in response to high pressure.

1. This imparts ***acute stretch*** on the vessel wall.
2. The **smooth muscles** of the blood vessels **relax in response to sudden stretch**.
3. This decreases vascular tone and **lowers pressure**.

Reverse Stress Relaxation: Reverse stress relaxation occurs *when blood pressure decreases*. Acute fall in blood pressure ***reduces the normal stretch of the vascular smooth muscle***. This in turn **causes contraction of smooth muscle** and increases vascular tone, which increases blood pressure.

Hormonal Mechanisms

There are many hormones and chemicals that change blood pressure by causing either vasodilation or vasoconstriction **(Table 55.1)**.

Catecholamines

In acute hypotension, stimulation of **sympathetic fibers to adrenal medulla** releases catecholamines.

1. Catecholamines (especially, norepinephrine) are vasoconstrictors.
2. They also increase heart rate and cardiac output. Thus, catecholamines **increase blood pressure** (for details, see chapter "Adrenal Medulla").
3. They increase blood pressure within minutes.
4. Catecholamines are injected as life-saving drugs in acute hypotension.

Renin-angiotensin System

Fall in blood pressure stimulates release of **renin from the Juxtaglomerular (JG) cells** of the kidney. Renin converts angiotensinogen to angiotensin I, which is further converted to **angiotensin II** by angiotensin-converting enzymes.

1. Angiotensin II is a **potent vasoconstrictor** that increases blood pressure.
2. Angiotensin II **increases synthesis and secretion of aldosterone**, which increases sodium and water reabsorption from kidney.
3. Angiotensin II stimulates thirst to increase water intake.
4. It also increases **water reabsorption** from kidney by its direct action on proximal convoluted tubule (for details, *refer* RAS in Chapter 95).
5. Renin-angiotensin-aldosterone system is more involved in long-term regulation of BP.

Vasopressin

Decrease in blood pressure and blood volume increases the **release of arginine-vasopressin** or antidiuretic hormone (ADH) from posterior pituitary.

1. ADH **increases water reabsorption** from kidney that restores blood volume and pressure.
2. ADH also **causes vasoconstriction** in supraphysiological concentration (for details, see the chapter 110 "Posterior Pituitary").

Table 55.1: Vasodilators and vasoconstrictors.

	Vasodilators	Vasoconstrictors
A. Circulating neurohumoral factors		
1	Histamine	Norepinephrine
2.	Epinephrine in skeletal muscle and liver	Epinephrine, except in skeletal muscle and liver
3.	Atrial natriuretic peptide (ANP)	Angiotensin II
4.	Substance P	Arginine vasopressin (ADH)
5.	Calcitonin gene-related protein (CGRP) α	Endogenous digitalis-like substance (EDLS)
6.	Vasoactive intestinal polypeptide (VIP)	Neuropeptide Y
B. Endothelial products		
1.	Nitric oxide (EDRF)	Endothelin 1
2.	Kinins (Bradykinin)	Serotonin (released from platelet
3.	Prostacyclin	Thromboxane A_2
C. Neural factors		
1.	Decreased discharge of sympathetic nerves	Increased discharge of sympathetic nerves
2.	Activation of β_2 adrenoceptors on the vasculature of skeletal muscles	
D. Local factors		
1.	Increased temperature	Cold
2.	Hypercapnia (increased CO_2), Hypoxia (decreased O_2)	Local autoregulation
3.	Increased K^+	
4.	Adenosine	
5.	Lactate	
6.	Decreased local pH (acidosis)	

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) is **secreted from atrial myocytes** in response to stretch. **Increased atrial filling** due to increased venous return stimulates secretion of ANP.

1. ANP produces **diuresis and natriuresis** that decreases blood volume (for details, see Chapter 120 "Local Hormones").
2. ANP also causes **vasodilation** that decreases blood pressure.

EDLS

Endogenous digitalis-like substances (EDLS) or factors (**EDLF**) are **naturally occurring steroids**, such **as ouabain** produced by the adrenal cortex and hypothalamus that regulate blood pressure and sodium balance.

They **inhibit Na^+, K^+-ATPase causing vasoconstriction and natriuresis**, and are involved in hypertension, heart failure, and pre-eclampsia.

Kallikrein-Kinin System

Kinins that cause vasodilation are bradykinin and lysyl bradykinin. Physiologically, kinins resemble histamine.

Bradykinin

Bradykinin is formed from high molecular weight kininogen by the action of plasma kallikrein, which is formed from

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prekallikrein. Activated factor XII (Hageman factor) of clotting system acts on prekallikrein to convert it into plasma kallikrein.

1. Bradykinin is a potent **vasodilator** and **decreases blood pressure**. It is part of short-term regulation of BP.
2. Bradykinin relaxes smooth muscle of blood vessels via nitric oxide.
3. Bradykinin also **increases capillary permeability** and facilitates chemotaxis.

Lysyl Bradykinin

Lysyl bradykinin is formed from low molecular weight kininogen by the action of tissue kallikrein. Tissue kallikrein is present in pancreas, kidney, intestine, salivary glands, and prostate, and in many other tissues.

1. **Tissue kallikrein** is located in the apical membrane of cells in these tissues and is involved primarily in transcellular electrolyte transport.
2. **Lysyl bradykinin** *increases tissue blood flow* and mediates local inflammatory response.

Histamine

Histamine is a **potent vasodilator** and therefore, instantaneously **decreases blood pressure.**

1. It is involved in short-term regulation of BP.
2. It is secreted from mast cells. During **anaphylactic reactions**, histamine is released by degranulation of mast cells that causes **acute hypotension** (for details, see chapter 120 "Local Hormones").

Endothelins

There are 3 different types of endothelins: endothelin type 1, type 2, and type 3. Endothelin 1 is formed from big-endothelin 1, which also possesses endothelin activity.

1. **Endothelin 1** is the most ***potent vasoconstrictor*** known so far. *Veins are more sensitive* to endothelin 1 than arteries.
2. It is also a potent positive chronotropic and inotropic agent (increases heart rate and myocardial contractility).
3. Thus, it **increases blood pressure** by causing vasoconstriction and increasing cardiac output.

Endothelium-derived Relaxing Factor

Endothelium-derived relaxing factor (EDRF) is the **nitric oxide** (NO) synthesized from arginine in the endothelial cells of blood vessels.

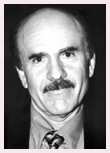
1. NO produces **relaxation of vascular smooth muscle** and **decreases blood pressure.**
2. In fact, NO mediates the action of many vasodilator substances.
3. Tonic release of NO is essential for maintaining normal BP, and NO deficiency results in hypertension.
4. NO is also involved in vascular remodeling and angiogenesis, and in the pathogenesis of atherosclerosis.

NO-dependent Vasodilators: **Histamine** (at H_1 receptors), **acetylcholine, bradykinin, VIP and substance P** depend on EDRF for producing vasodilation. However, *ANP and adenosine* ***do not depend*** *on EDRF* for their vasorelaxation effect.

Scientists contributed



Robert F Furchgott



Louis J Ignarro



Ferid Murad

The **Nobel Prize in Physiology or Medicine 1998** was awarded jointly to three American cardiovascular physiologists **Robert F Furchgott, Louis J Ignarro, and Ferid Murad** *"for their discoveries concerning* ***nitric oxide*** *as a signaling molecule in the cardiovascular system".*

Adrenomedullin

Adrenomedullin is a polypeptide hormone secreted from adrenal medulla. It was first discovered in pheochromocytoma cells.

1. It **causes vasodilation** by increasing the synthesis of nitric oxide.
2. Adrenomedullin decreases blood pressure and **inhibits aldosterone synthesis.**
3. Adrenomedullin is synthesized from **proadrenomedullin**, which also causes vasodilation by decreasing peripheral sympathetic activity.

Long-term Regulation of BP

Long-term regulation of blood pressure occurs by **renal and hormonal mechanisms** that primarily involve ***change in fluid volume*** of the body. However, neural mechanisms also contribute in the process.

1. **Renal mechanism** is the role of kidney in control of blood volume and pressure by altering two primary processes, the ***pressure diuresis and pressure natriuresis.***
2. **Hormonal mechanism** is mainly the ***renin-angiotensin-aldosterone system***, in which angiotensin and aldosterone regulate blood volume, and pressure by controlling salt and water reabsorption from kidney.
3. **Neural mechanisms** are ***resetting of baroreceptor reflex*** in response to long-term elevation of blood pressure and contribution of **sympathovagal balance** in the long-term regulation of blood pressure.

Renal Mechanisms

Kidney controls blood volume by controlling **urinary excretion of salt and water**. With alteration in blood pressure changes the ***rate of excretion of sodium and water*** by kidneys that tend to restore blood pressure over days and weeks.

Pressure Diuresis and Natriuresis

With increase in arterial pressure from 60 to 200 mm Hg, there is progressive in water excretion (**pressure diuresis**) and sodium excretion (**pressure natriuresis**) in urine **(Fig. 55.14)**.

1. The curve depicting the relationship between arterial pressure and urinary excretion is called **renal output curve**. The renal output curve is less steep from 60 to 120 mm Hg and more-steep from 120 to 200 mm Hg.

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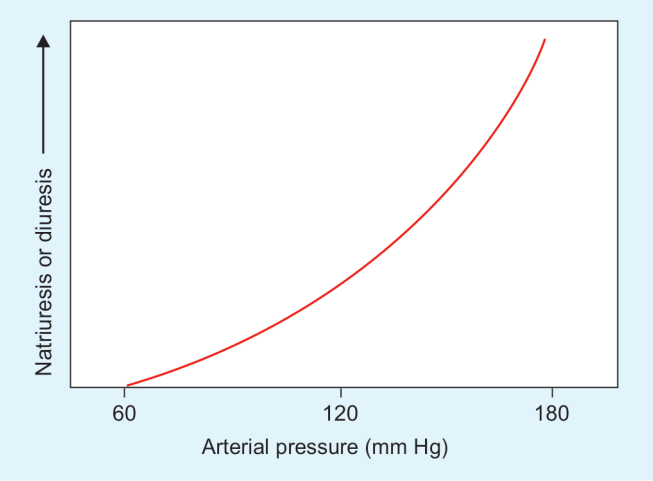


Fig. 55.14: Intrinsic natriuresis and diuresis in response to chronic increase in mean arterial pressure (MAP).

2. It is suggested that pressure diuresis and natriuresis are **intrinsic properties of the kidney** to control blood volume and blood pressure.

Salt Content is the Major Determinant

The major determinant of long-term arterial pressure level in human being is the salt content of plasma.

Salt Intake

It has been well-established that more salt intake is the main cause of chronically elevated blood pressure. Therefore, restriction of salt is the mainstay of treatment of hypertension and heart disease. Hypertension is not seen in tribes not eating salt **(Application Box 55.2)**.

Application Box 55.2

Hypertension never occurs in tribes not eating salt: Numidian nomads and certain Bedouins who feed on fish and roasted meat, never eat salt with food have reported to be free from hypertension. Eskimos who have not been in contact with Western civilization had a strong dislike for salt and would even avoid food in which saltiness could be detected. Hypertension is rare in Eskimos.

Salt Preference and Sensitivity

The contribution of **salt preference and sensitivity** to essential hypertension in humans and experimental hypertension in animal models is well-established.

1. **Salt preference** is the more liking for salt in food, which is more of a social and cultural development, though heredity also plays a role in it. Individuals with ***salt preference are more prone to hypertension*** due to their increased salt intake.
2. **Salt sensitivity** is the rise in blood pressure due to more response of blood vessels to salt in the body. Those who are more sensitive to salt, they tend to have ***more salt retention and develop hypertension*** even at normal salt level in their blood. But, usually people with salt preference are also more salt sensitive.
3. Recent studies indicate the close link of **salt sensitivity to sympathetic activity**. It has been reported that excess salt intake leading to salt retention increases the production of **endogenous digitalis-like factors** (EDLFs) that act centrally to ***increase sympathetic outflow***, *increase myocardial contractility to increase cardiac output*, and cause ***proliferation of arterial smooth muscle and promote their contraction***; all these factors contribute to the genesis of hypertension.
4. **Known EDLFs** are ouabain, digoxin, marinobufagenin, marinobufotoxin, telocinobufagin, proscillaridin A and bufalin. These chemicals have a steroid nucleus ***and they promote contraction of vascular smooth muscle and myocardium by inhibiting*** Na^+–K^+ ATPase. Hence, they are also grouped as **cardiotonic steroids**. Increased levels of EDLFs have been reported to **increase BP in salt-retaining individuals**.

Hormonal Mechanisms

Hormones that are involved in long-term control of blood pressure are **aldosterone, ADH, and ANP**. These hormones act on kidney to regulate water and sodium excretion.

Renin-angiotensin-aldosterone System

Fall in blood pressure increases release of renin that causes Angiotensin-II formation.

1. Angiotensin-II is a potent ***vasoconstrictor*** and a potent stimulator for **secretion of aldosterone**.
2. **Aldosterone** increases ***sodium and water reabsorption*** from kidney and increases blood pressure by long-term mechanism.
3. Aldosterone is major long-term regulator of BP.

Antidiuretic Hormone

When blood volume decreases, ADH secretion from posterior pituitary increases.

1. Antidiuretic hormone **increases water reabsorption** from kidney and increases blood volume and pressure.
2. It also causes ***vasoconstriction*** in supraphysiological concentration.

Atrial Natriuretic Peptide

Increased blood volume increases venous return that increases synthesis of ANP in atrial myocytes. ANP causes **natriuresis and diuresis** that decreases blood pressure.

Neural Mechanisms

Baroreceptor Resetting and Central Adaptation

In chronic hypertension, **baroreceptors are reset** to regulate the elevated blood pressure. The firing rate of baroreceptors decreases in response to chronic hypertension. Medullary **cardiovascular centers also adapt** to elevated pressure.

Role of Sympathovagal Balance

Emotional responses of the body and responses to the environment are major stimuli for alteration in blood pressure. These responses are executed through sympathetic and the parasympathetic systems. The long-term BP regulation is the **product of sympathovagal balance**.

1. Failure to react or excess reactions, and persistent autonomic reactions to internal or environmental stresses lead to sympathovagal imbalance and rise in blood pressure.

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2. As blood vessels of systemic vasculature are innervated exclusively by sympathetic vasoconstrictor fibers, **chronic sympathetic hyperactivity** is the primary pathophysiological mechanism for essential hypertension. Also, chronic increase in sympathetic tone causes thickening of the vessel wall and increases vascular reactivity.
3. It has been reported recently (by *GK Pal et al.*) that **vagal withdrawal** is associated with sympathetic overactivity resulting in sympathovagal imbalance and **vagal inhibition plays a bigger role in the genesis of prehypertension and hypertension** (*Future Cardiology. 2013;9:53-69*).
4. Vagal control has been reported to play a bigger role in long-term regulation of blood pressure through its profound effects on regulation of heart rate and cardiac output. Therefore, **vagal inhibition** is crucial in the genesis of hypertension.

Thus, long-term regulation of blood pressure is a neural–vascular–humoral mechanism, in which autonomic modulation plays a crucial role in determining the vasomotor tone.

CHAPTER SUMMARY

- Smooth muscles of blood vessel, like other smooth muscles normally exhibit tone, *a state of prolonged partial contraction.* BP is mostly influenced by the vascular tone (**tone of blood vessels)**, especially *of the resistance vessels* (arterioles and small arteries).
- As BP is the product of cardiac output and peripheral resistance, factors that influence cardiac output or peripheral resistance affect the blood pressure. Alteration in **cardiac output mainly affects systolic pressure** and alteration in **peripheral resistance mainly affects diastolic pressure**.
- **Short-term regulation** of BP is mainly neural mechanism, though the vascular and hormonal mechanisms also contribute to it.
- **Sympathetic regulation** is the main control mechanism for BP regulation as the sympathetic fibers are the **final pathways** of all neural inputs to the blood vessels. There is no parasympathetic innervation of blood vessel in general circulation.
- Stimulation of sympathetic fibers *produces vasoconstriction* and therefore they are called vasoconstrictor fibers. Sympathetic vasoconstrictor fibers have the **basal rate of tonic discharge**, which is essential for maintaining the normal vascular tone. Thus, the vascular sympathetic tone is also known as **sympathetic vasoconstrictor tone**.
- **Medullary cardiovascular centers** are (i) vasomotor center and (ii) cardioinhibitory center. RVLM is the main part of VMC. **Stimulation of VMC** (RVLM) in the medulla results in sympathetic activation. The basal tonic sympathetic vasoconstrictor tone is due to the drive of preganglionic sympathetic neurons by the **tonic discharge of VMC neurons**.
- Cardioinhibitory center in the medulla is formed by nucleus tractus solitarius (NTS), nucleus ambiguous, and dorsal motor nucleus of vagus. Stimulation of these areas results in **bradycardia and decreased cardiac output** by two mechanisms. **NTS inhibits RVLM** (VMC).
- **Baroreceptor reflex** works within a wide range and is the first reflex to be activated by rise in BP (deactivated by fall in BP). Among all the cardiovascular reflexes, most important is the baroreceptor reflex as it *regulates blood pressure within seconds*. Baroreceptor reflex is therefore a life-saving reflex.
- Baroreceptor reflex explains the physiological basis for **Marey's Law**, which states that *heart rate is inversely proportional to blood pressure* (but not the vice versa).
- The range of regulation of blood pressure by **chemoreceptor reflex** is 40–70 mm Hg. **Cushing reflex** is the last reflex to increase BP in severe hypotension and hemorrhage.
- When **intracranial pressure (ICP) is high**, as occurs in brain tumor, hypoxic stimulation of vasomotor center and causes intense vasoconstriction that in turn *increases blood pressure.* This is known as Cushing reflex. The increase in BP in carotid sinus *activates baroreceptor reflex* and causes reflex bradycardia. Therefore, bradycardia occurs in brain tumors.
- The **vascular mechanisms** operate within seconds to minutes of alteration in blood pressure. These are *capillary fluid shift* and *stress relaxation*.
- **Vascular endothelium** plays a big role by secreting vasoactive substances such as endothelins, EDRF, kinins, thromboxane A_2, etc. Histamine (at H_1 receptors), acetylcholine, bradykinin, VIP and substance P depend on EDRF for producing vasodilation. However, ANP and adenosine *do not depend* on EDRF for their vasorelaxation effect.
- **Long-term regulation** of BP is mainly by renal, hormonal, and baroreceptor resetting mechanisms. Kidney controls blood volume and pressure by controlling **urinary excretion of salt and water**.

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Gopal Krushna Pal MBBS MD (Physiology) PhD DSc BNYT MD (Alt Med) MD (Yoga) DSc (Hon Causa) MABMS FABMS FABAP FSAB FRSB (UK) FIABS FEFI FAPI is a Professor (Senior Scale) in JIPMER, Puducherry, India. He is a Gold Medalist in Medicine and recipient of Shyamabati Dubey Award for outstanding performance in MBBS, opted to become a Physiologist by choice and predilection. A dedicated teacher, renowned author, and a researcher par excellence, he has received 27 national research awards in Physiology, which include ICMR Scientist Award for Biomedical Research, Dr DS Munagekar Award of Indian Medical Association (IMA), Dr BK Anand Award, Professor RC Shukla Oration Award, ML Gupta Prize, AV Tilak Parvathy Devi Prize, Sushila Thaker Prakriti Mandir Prize, KP Puthuraya Best Teacher Award of Association of Physiologists and Pharmacologists of India (APPI), Dr N Padmanabhan Memorial Award, SIRI Research Award, Professor A Namasivayam Award, SS Memorial Oration Award of Indian Association of Biomedical Scientists (IABMS), Professor JN Maitra Memorial Oration Award of the Physiological Society of India (PSI), and Professor RN Sen Memorial Oration Award of APO, MK Nambiar Oration of IABMS, Padmashree CP Thakur Best Teacher Oration, Maj Gen SL Bhatia Oration and IGIMS External Faculty Oration, Outstanding Physiologist Oration and AS Paintal Oration of ASSOPI, DSc Honorie Causa of Amity University, and VK Shrivastava Oration of Epidemiology Foundation of India. He was Executive Director, AIIMS, Patna, and for his outstanding contributions for the overall development, AIIMS, Patna was rated among the Best 100 Global Hospital Award 2023, and out of 818 medical colleges in the country, for the first time AIIMS, Patna secured 27th position among top 50 in NIRF Ranking and got the National Kayakalp Award 2023. He has more than 235 indexed research publications, scientist h-index 34, i-10 index 80, citations 4,091, and research reads 48,907. He was awarded five-advance increments in salary by UPSC for his outstanding performance in selection for JIPMER Faculty post in 1996, an unparallel record in history of UPSC. He has the distinction of starting DM Course in Clinical and Interventional Physiology in India in 2023.

Pravati Pal MBBS MD (Physiology) MABMS BNYT MD (AM) is a Professor (Senior Scale) in the Department of Physiology, JIPMER, Puducherry, India, and has an outstanding educational and research career. She is the recipient of Gauri Shankar Memorial Award for securing highest rank in HSC Examination in the state of Odisha. For brilliant performance in MD examination, she was awarded Distinction, Gold Medal, and Vaithilingam Venkatasubba Reddiar Medal of Pondicherry University. For her best research work, she was awarded Dr N Padmanabhan Memorial Award of IABMS, Niranjan Bishnupriya Award of APO, and Professor KP Puthuraya Award of APPI for the best teacher in Physiology. For her outstanding professorship, she was awarded Shiksha Ratna Puraskar of IIFS.

Nivedita Nanda MSc PhD (Medical Biochemistry) BNYT is a Professor in the Department of Biochemistry, Faculty I/C of central research facilility and core-team member of NTTC, JIPMER, Puducherry, India. She has an excellent academic and research record. She was among the best-tenth rank holders in HSC Examination, Odisha. She was awarded Dr N Padmanabhan Memorial Award of IABMS for best PG research work, Professor GK Pal Award of APPI for best research publication in IJPP, Young Biomedical Scientist Award of ABAP, and Shri BM Patil Memorial Award of ASSOPI for best research publication by a scientist below 45 years, for the year 2018. For her outstanding academic contribution, she was awarded Shiksha Ratna Puraskar of IIFS. She is a FAIMER Fellow.

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