Pathophysiology

Cardiovascular disorders

Disorders of the Arterial Circulation

- The arterial system delivers oxygen and nutrients to the tissues.

■ Disorders of the arterial circulation produce ischemia owing to narrowing of blood vessels, thrombus formation associated with platelet adhesion, and weakening of the vessel wall.

■ Atherosclerosis is a progressive disease characterized by the formation of fibrofatty plaques in the intima of large and medium-sized vessels, including the aorta, coronary arteries, and cerebral vessels. The major risk factors for atherosclerosis are hypercholesterolemia and inflammation.

Disorders of the Arterial Circulation

■ Vasculitis is an inflammation of the blood vessel wall resulting in vascular tissue injury and necrosis. Arteries, capillaries, and veins may be affected. The inflammatory process may be initiated by direct injury, infectious agents, or immune processes.

■ Aneurysms represent an abnormal localized dilatation of an artery due to a weakness in the vessel wall. As the aneurysm increases in size, the tension in the wall of the vessel increases and it may rupture. The increased size of the vessel also may exert pressure on adjacent structures.

Hyperlipidemia and Atherosclerosis

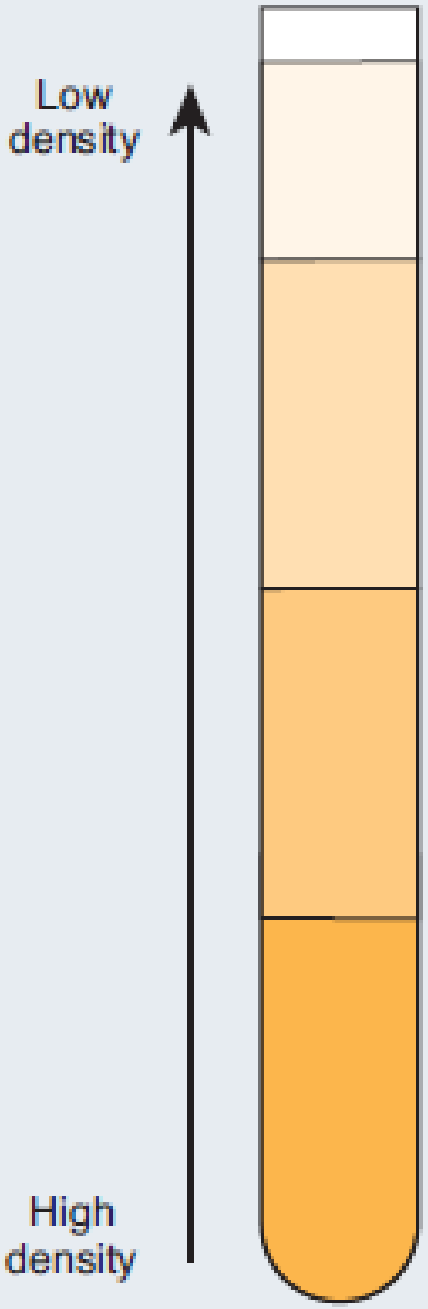
Hyperlipidemia with its associated risk for development of atherosclerosis is a major cause of cardiovascular disease. Atherosclerosis causes more morbidity and mortality in the Western world than any other disorder. By the year 2025, it is predicted that cardiovascular mortality will likely exceed that of every other major disease group including infections, cancer, and trauma.

Hyperlipidemia

Because lipids, namely, cholesterol and triglycerides, are insoluble in plasma, they are encapsulated by special fatcarrying proteins called lipoproteins for transport in the blood. There are five main types of lipoproteins, classified by their densities, which reflect their protein content:

- chylomicrons, very-low-density lipoprotein (VLDL),
- intermediate-density lipoprotein (IDL),
- low-density lipoprotein (LDL),
- and high-density lipoprotein (HDL).

VLDL carries large amounts of triglycerides that have a lower density than cholesterol. LDL is the main carrier of cholesterol, whereas HDL is about 50% protein and carries less cholesterol


Low
density
High
density
Chylomicrons
80% – 90% triglycerides,
2% protein
VLDL
55% – 65% triglycerides,
10% cholesterol,
5% – 10% protein
LDL
10% triglycerides,
50% cholesterol,
25% protein
HDL
5% triglycerides,
20% cholesterol,
50% protein

Hypercholesteremia

Hypercholesteremia refers to increased levels of cholesterol in the blood. Blood cholesterol in adults can be described according to the classification system of the Third Report of the National Cholesterol Educational Program (NCEP) Expert Panel on Detection, Evalua
describes optimal to very high levels of LDL chole
cholesterol

LDL Cholesterol	
<100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Hypercholesteremia

Cholesterol is carried in the blood as VLDL, LDL, and HDL, with the total cholesterol being equal to the sum of these three components.

Most clinical laboratories measure the total serum cholesterol, total triglycerides, and the amount of cholesterol carried in the HDL fraction. The LDL is then estimated by subtracting the HDL from the total serum cholesterol and the triglycerides divided by 5* (i.e., LDL [mg/dL] =total cholesterol [mg/dL] -HDL [mg/dL] -triglycerides [mg/dL]/5)

Hypercholesteremia

Thus, serum cholesterol levels may be elevated as a result of an increase in any of the lipoproteins. For example, two persons with the same total cholesterol of 275 mg/dL may have very different lipid profiles. One person may have a favorable lipid profile with an HDL of 110 mg/dL, a triglyceride level of 175 mg/dL, and an LDL of 130 mg/dL, whereas another person with an HDL of 40 mg/dL, a triglyceride level of 150 mg/dL, and an LDL cholesterol of 205 mg/dL would be at much greater risk for cardiovascular disease.

Hypercholesteremia

- Several factors, including nutrition, genetics, comorbid conditions, medications, and metabolic diseases, can raise blood lipid levels.
- Hypercholesterolemia can be divided into two types: primary or secondary.
- Primary hypercholesterolemia describes elevated cholesterol levels that develop independent of other causes,
- Secondary hypercholesterolemia is associated with other health problems and behaviors.

Hyperlipidemia take home message?

- Life style
- Diet
- Antihyperlipidemics

Atherosclerosis

Atherosclerosis is a type of arteriosclerosis or hardening of the arteries. The term atherosclerosis, which comes from the Greek words atheros ("gruel" or "paste") and sclerosis ("hardness"), denotes the formation of fibrofatty lesions in the intimal lining of the large and medium-sized arteries such as the aorta and its branches, the coronary arteries, and the cerebral arteries that supply the brain. The disorder remains a leading cause of coronary artery disease, stroke, and peripheral artery disease.

Atherosclerosis

CHART 18-1 Risk Factors for Atherosclerosis

Nonmodifiable

- Increasing age
- Male gender
- Genetic disorders of lipid metabolism
- Family history of premature coronary artery disease

Potentially Modifiable

- Cigarette smoking
- Obesity
- Hypertension
- Hyperlipidemia with elevated low-density lipoprotein and low high-density lipoprotein cholesterol
- Diabetes mellitus

Additional Nontraditional

- Inflammation marked by elevated C-reactive protein levels
- Hyperhomocystinemia
- Increased lipoprotein (a) levels

Development of Atherosclerosis

Atherosclerosis is characterized by the development of atheromatous lesions within the intimal lining of the large and medium-sized arteries that protrude into and can eventually obstruct blood flow. The development of atherosclerotic lesions is a progressive process involving

(1) endothelial cell injury,

(2) Migration of inflammatory cells,

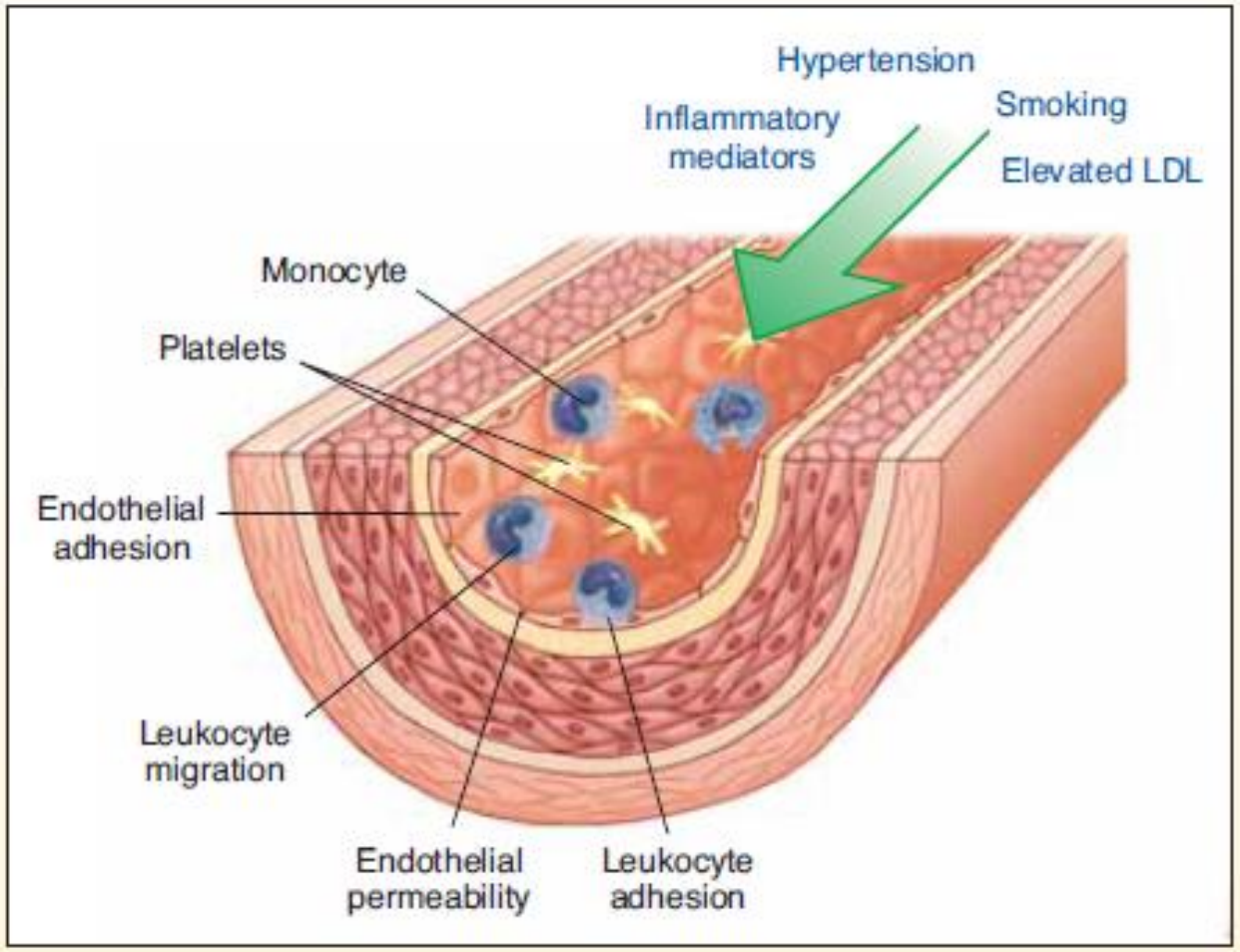
(3) smooth muscle cell proliferation and lipid deposition, and

(4) gradual development of the atheromatous plaque with a lipid core.

Development of Atherosclerosis

1

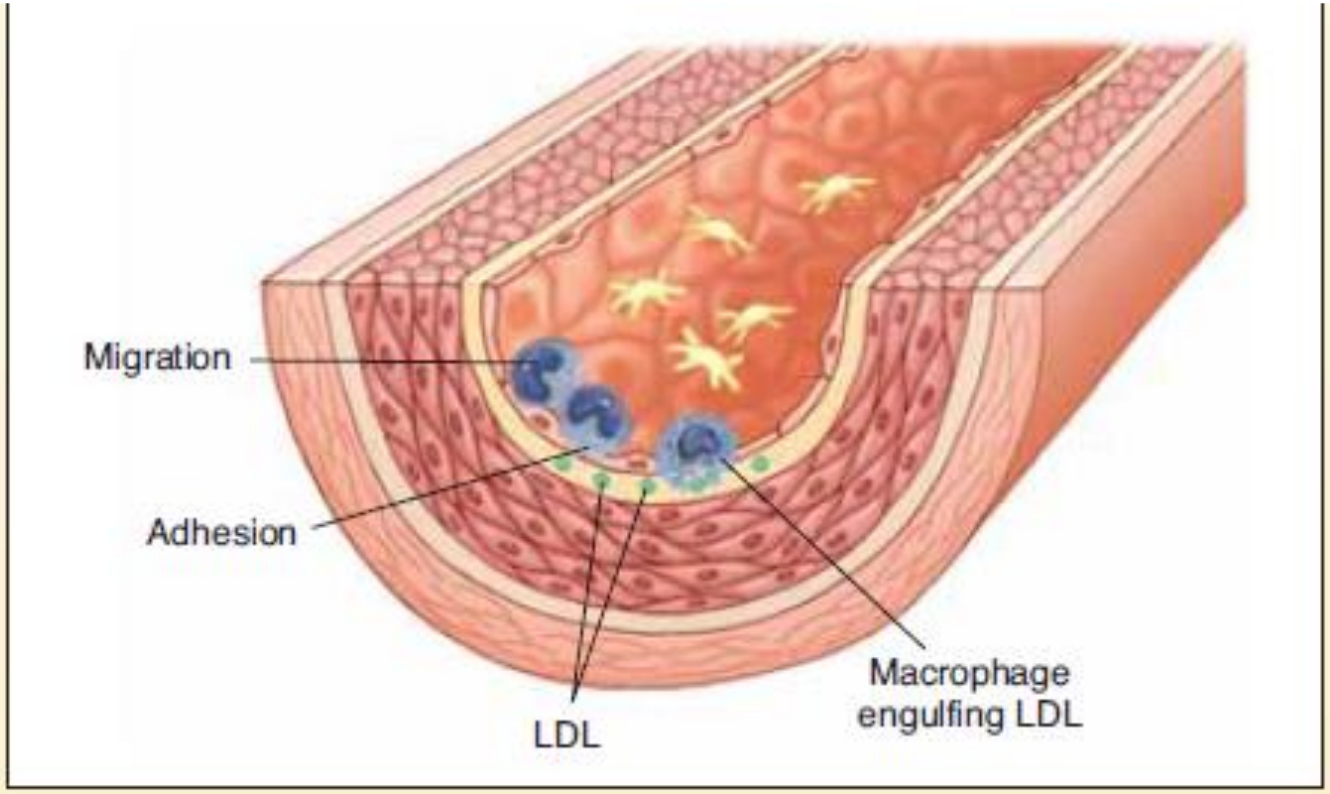
Endothelial Cell Injury. The vascular endothelium consists of a single layer of cells with cell-to-cell attachments, which normally protects the subendothelial layers from interacting with blood cells and other blood components. Agents such as smoking, elevated low-density lipoprotein (LDL) levels, immune mechanisms, and mechanical stress associated with hypertension share the potential for causing endothelial injury with adhesion of monocytes and platelets.



Development of Atherosclerosis

2

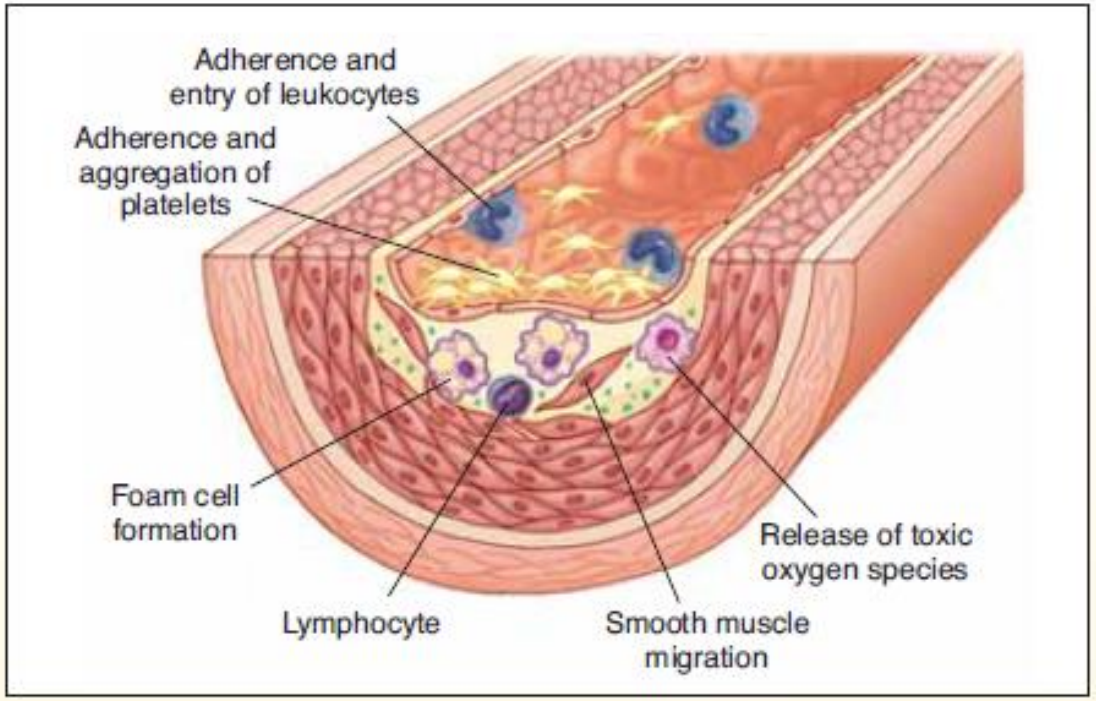
Migration of Inflammatory Cells. Early in the development of atherosclerotic lesions, endothelial cells begin to express selective adhesion molecules that bind monocytes and other inflammatory cells that initiate the atherosclerotic lesions. After monocytes adhere to the endothelium, they migrate between the endothelial cells to localize in the intima, transform into macrophages, and engulf lipoproteins, largely LDL.



Development of Atherosclerosis

3

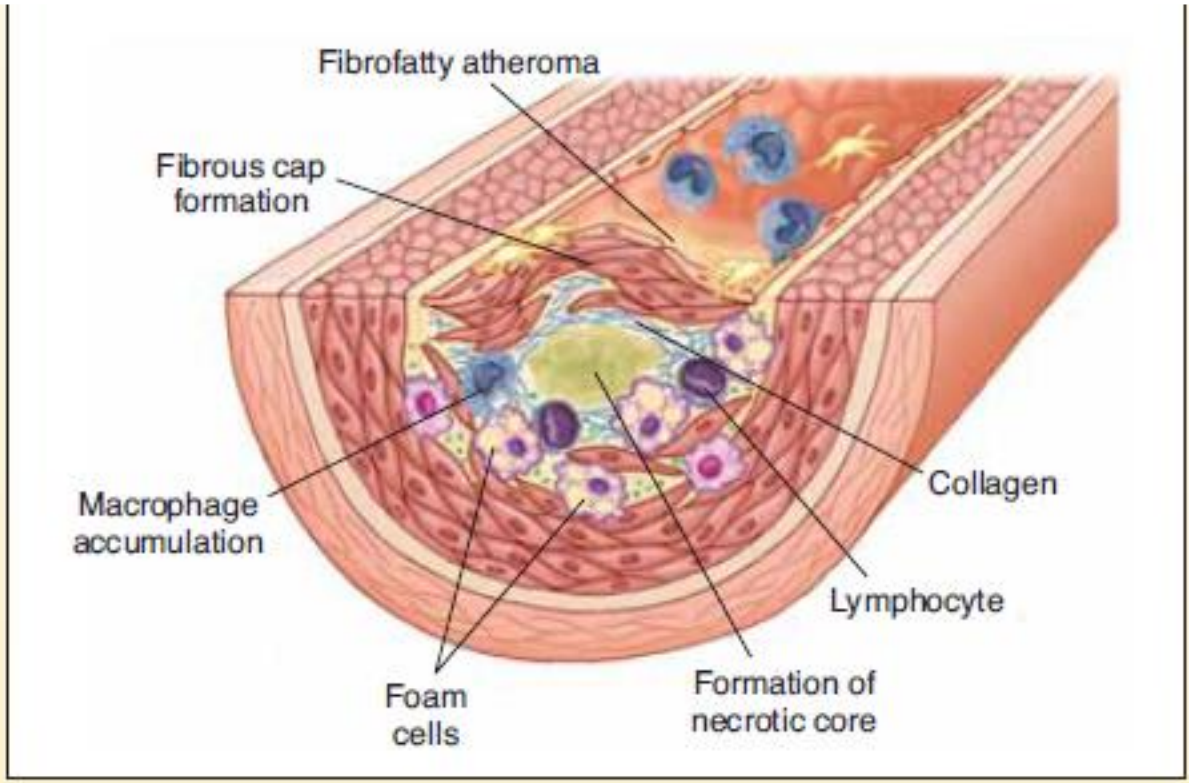
Lipid Accumulation and Smooth Muscle Cell Proliferation. Although the recruitment of monocytes to the arterial wall and their subsequent differentiation into activated macrophages that remove LDL from the circulation is protective, it also contributes to the development of atherosclerosis. Activated macrophages release toxic oxygen species that oxidize LDL. The oxidized LDL is then ingested by the macrophages through a scavenger receptor, which is distinct from the LDL receptor, resulting in the formation of foam cells, which are the primary component of atherosclerotic lesions. Activated macrophages also produce growth factors that contribute to the migration and proliferation of smooth muscle cells (SMCs) and the elaboration of extracellular matrix (ECM).



Development of Atherosclerosis

4

Plaque Structure. Atherosclerotic plaques consist of an aggregation of SMCs, macrophages, and other leukocytes; ECM, including collagen and elastic fibers; and intracellular and extracellular lipids. Typically, the superficial fibrous cap is composed of SMCs and dense ECM. Immediately beneath and to the side of the fibrous cap is a cellular area (the shoulder) consisting of macrophages, SMCs, and lymphocytes. Below the fibrous cap is a central core of lipid-laden foam cells and fatty debris. Rupture, ulceration, or erosion of an unstable or vulnerable fibrous cap may lead to hemorrhage into the plaque or thrombotic occlusion of the vessel lumen.

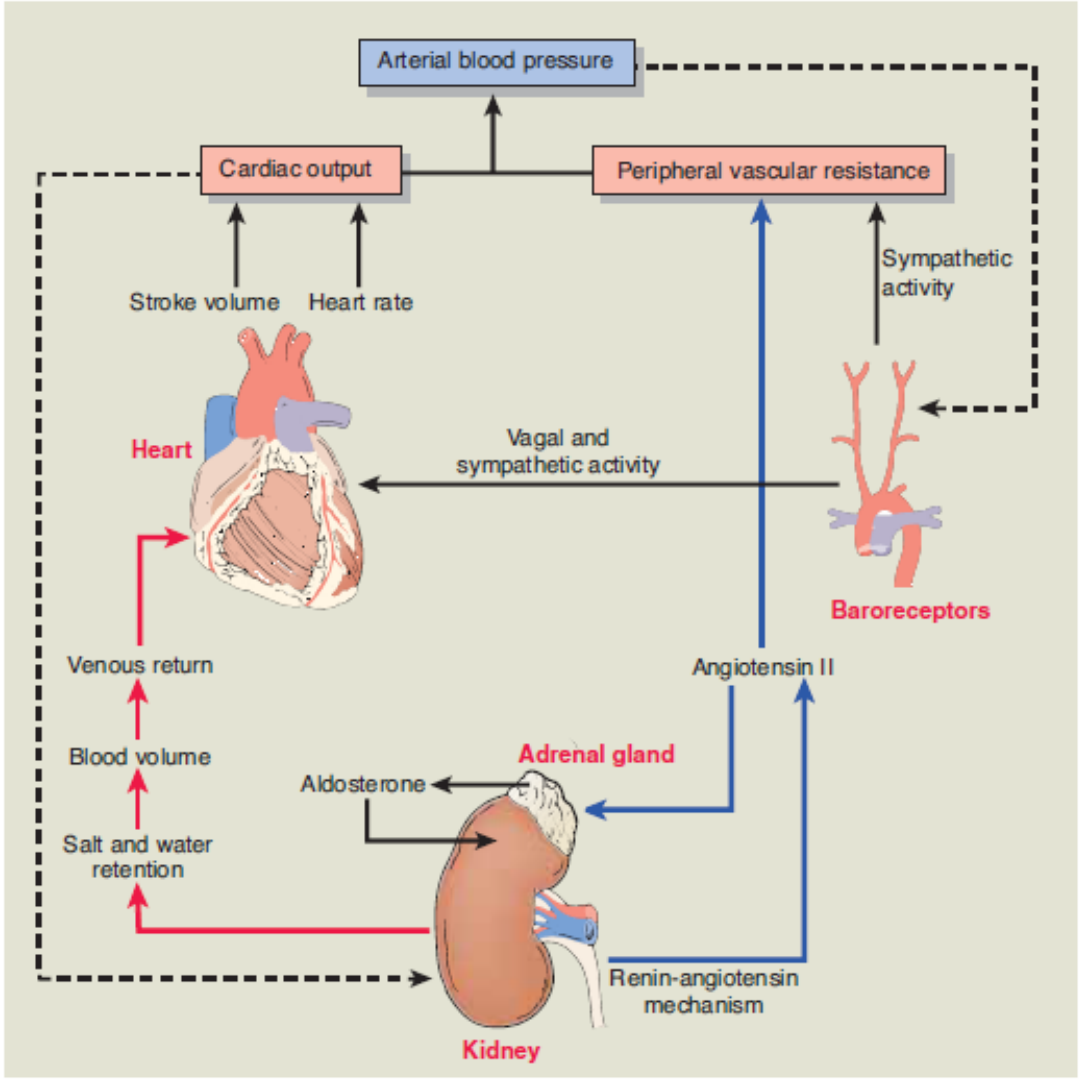


Atherosclerosis take home message?

- Life style
- Diet
- Antiyperlipidemics
- Antidiabetics
- Surgery

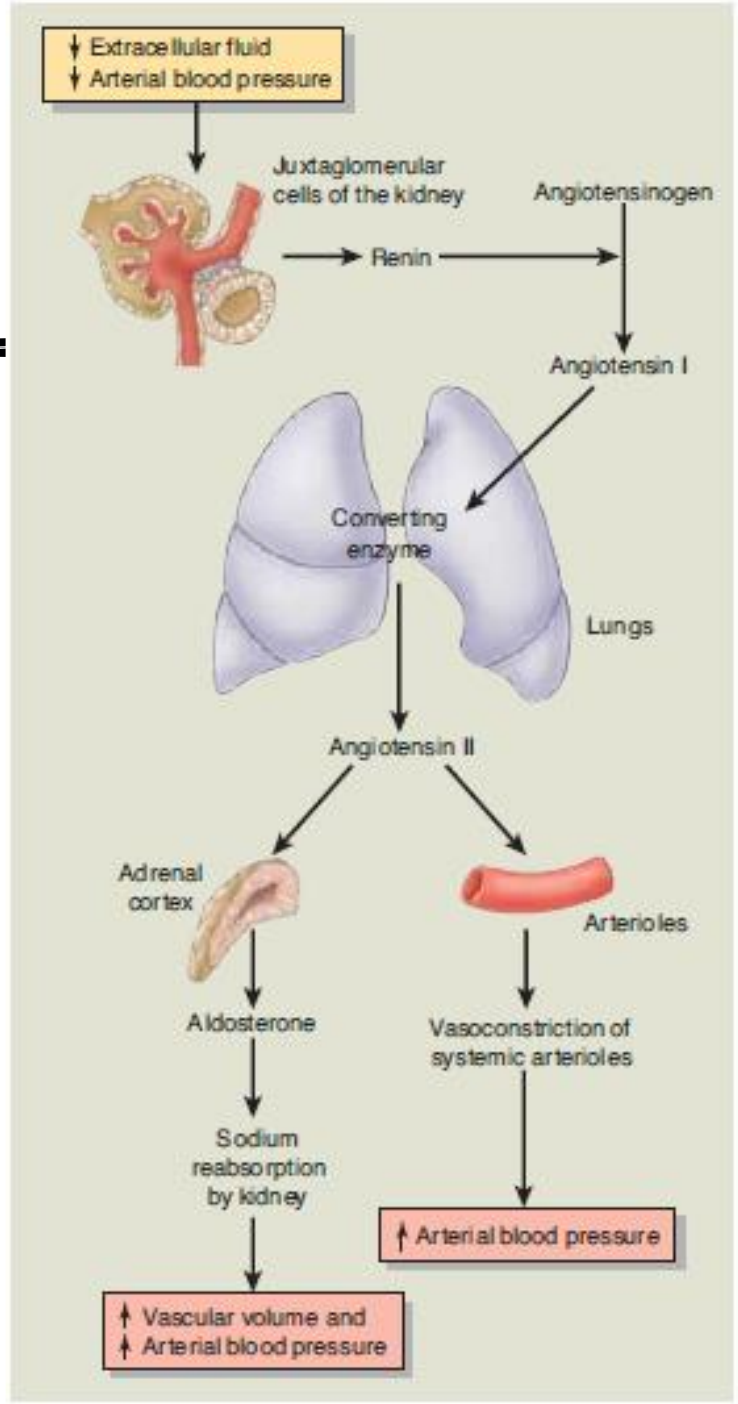
Hypertension

Mechanisms of blood pressure regulation. The solid lines represent the mechanisms for renal and baroreceptor control of blood pressure through changes in cardiac output and peripheral vascular resistance. The dashed lines represent the stimulus for regulation of blood pressure by the baroreceptors and the kidneys.



Hypertension

Control of blood pressure by the reninangiotensin-aldosterone system. Renin enzymatically converts the plasma protein angiotensinogen to angiotensin I; angiotensin-converting enzyme in the lung converts angiotensin I to angiotensin II; and angiotensin II produces vasoconstriction and increases salt and water retention through direct action on the kidney and through increased aldosterone secretion by the adrenal cortex.



Hypertension

- Hypertension represents an elevation in systolic and/or diastolic blood pressure.
- Primary or essential hypertension is characterized by a chronic elevation in blood pressure that occurs without evidence of other disease, and secondary hypertension by an elevation of blood pressure that results from some other disorder, such as kidney disease.

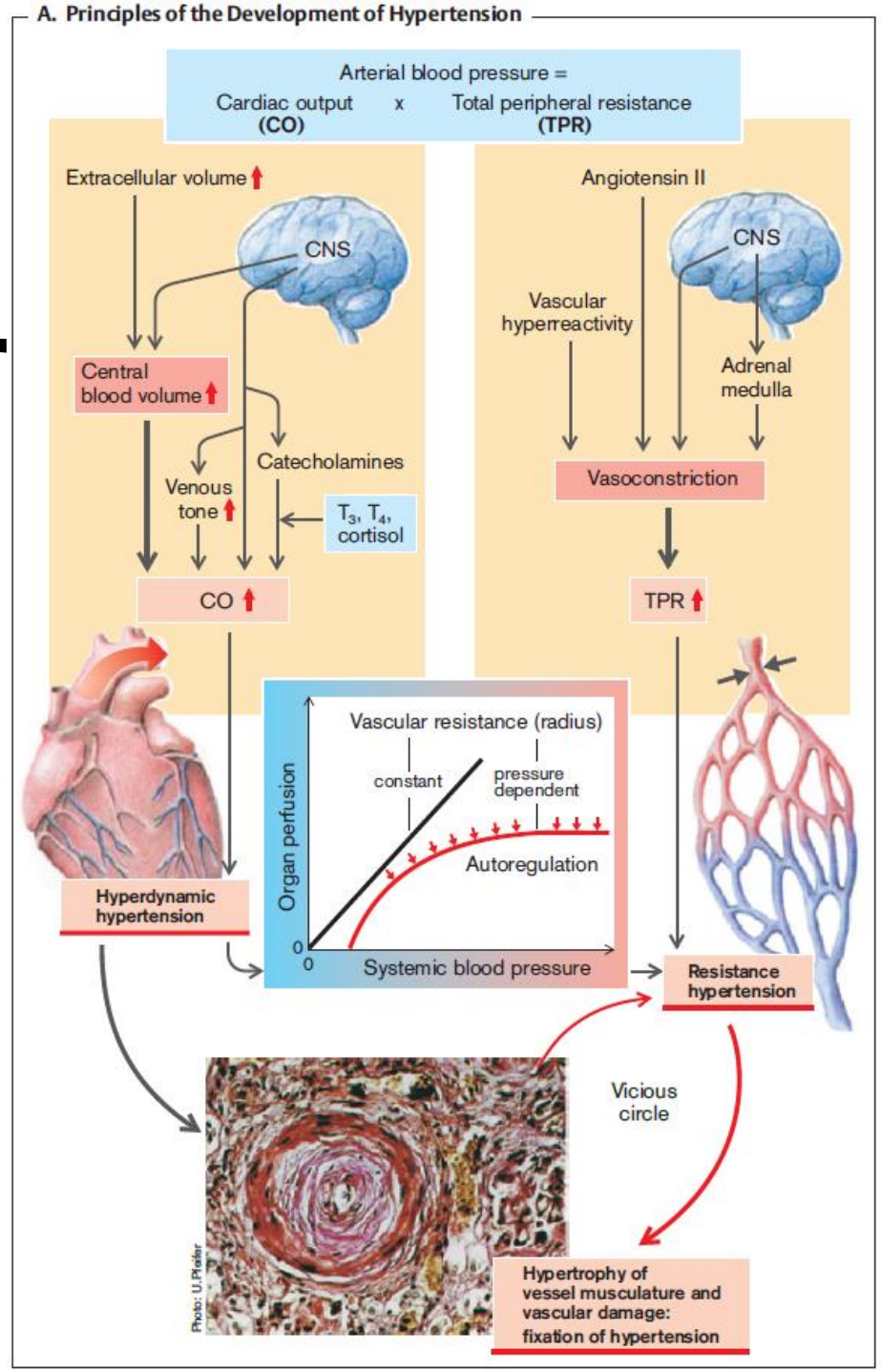
Hypertension

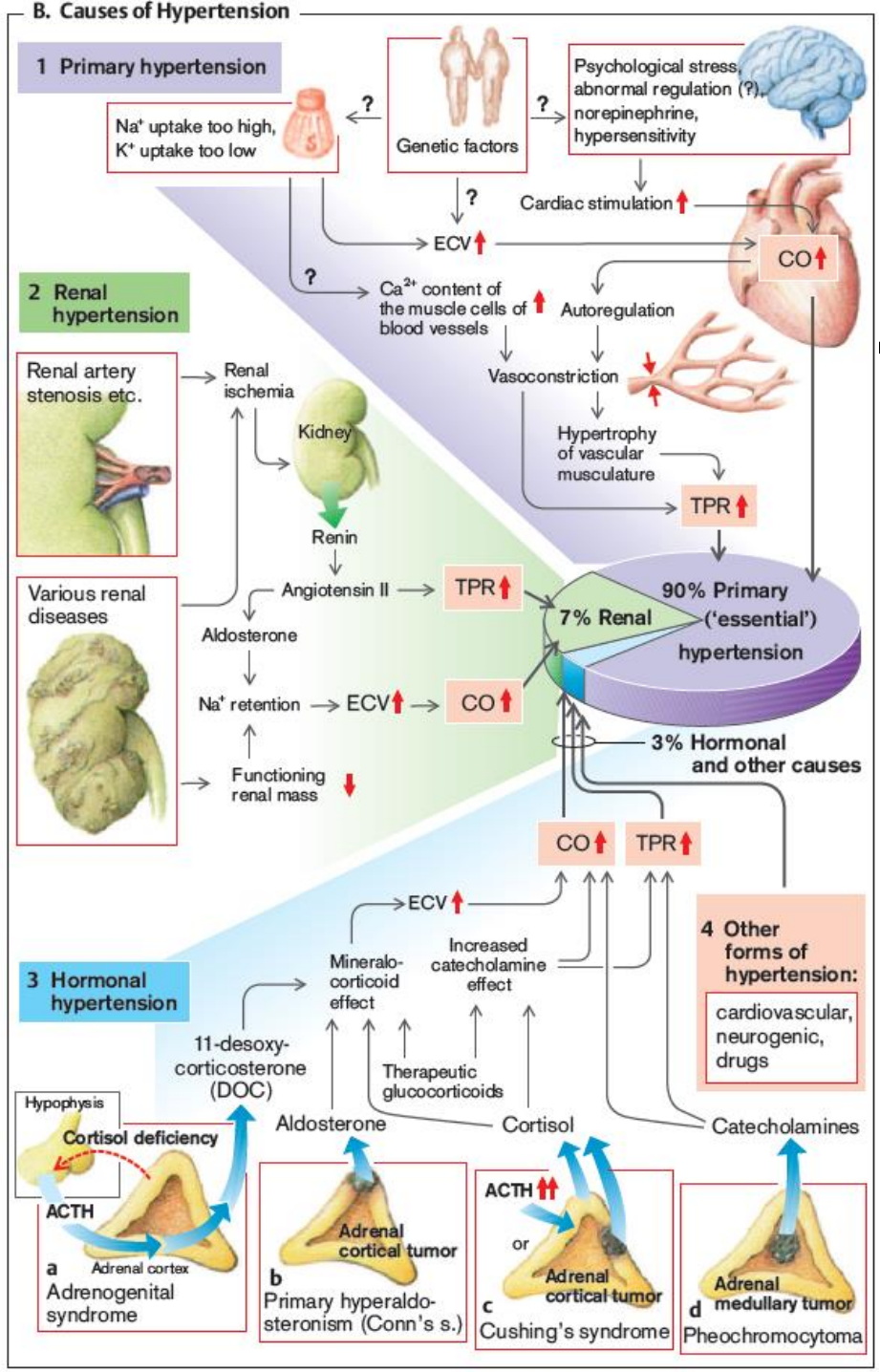
- The pathogenesis of essential hypertension is thought to include constitutional and environmental factors involving the kidney and its role in regulating extracellular fluid volume through salt and water elimination, sympathetic nervous system hyperreactivity, renin–angiotensin system activity, or intracellular sodium and calcium levels. The medications that are used in the treatment of hypertension exert their effect through one or more of these mechanisms.

- Uncontrolled hypertension produces increased demands on the heart, resulting in left ventricular hypertrophy and heart failure, and on the vessels of the arterial system, leading to atherosclerosis, kidney disease, retinopathy, and stroke.

Hypertension

Blood Pressure Classification	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Follow-up Recommendations for Initial Blood Pressure*†
Normal	<120	And <80	Recheck in 2 years
Prehypertensive	120–139	or 80–89	Recheck in 1 year‡
Stage 1 hypertension	140–159	or 90–99	Confirm within 2 months‡
Stage 2 hypertension	≥160	or ≥100	Evaluate or refer to source of care within 1 month. For those with higher pressure (e.g., >180/110 mm Hg), evaluate and treat immediately or within 1 week, depending on clinical situation and complications.


A. Principles of the Development of Hypertension
Arterial blood pressure =
Cardiac output (CO) x Total peripheral resistance (TPR)
Extracellular volume
CNS
Central blood volume
Venous tone
Catecholamines
T3, T4, cortisol
CO
Angiotensin II
CNS
Vascular hyperreactivity
Adrenal medulla
Vasoconstriction
TPR
Hyperdynamic hypertension
Vascular resistance (radius)
constant
pressure dependent
Autoregulation
Organ perfusion
0
0
Systemic blood pressure
Resistance hypertension
Vicious circle
Photo: U. Pfeiffer
Hypertrophy of vessel musculature and vascular damage: fixation of hypertension

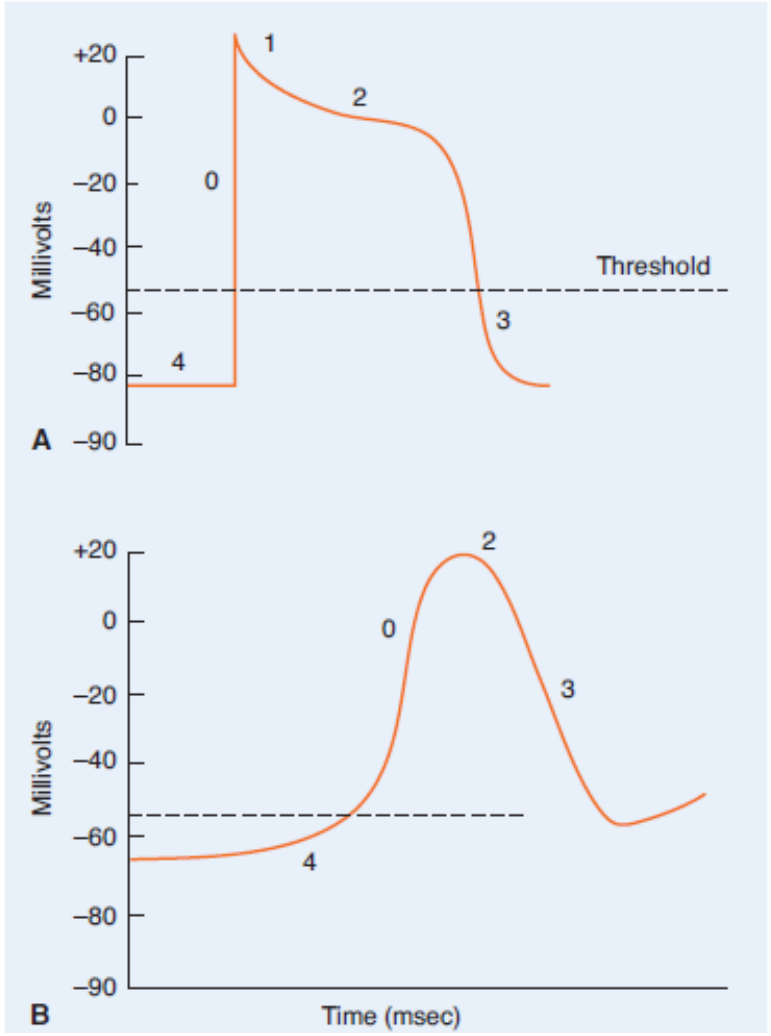

B. Causes of Hypertension
1 Primary hypertension
Na+ uptake too high, K+ uptake too low
Genetic factors
Psychological stress, abnormal regulation (?), norepinephrine, hypersensitivity
Cardiac stimulation
ECV
CO
2 Renal hypertension
Ca2+ content of the muscle cells of blood vessels
Autoregulation
Vasoconstriction
Hypertrophy of vascular musculature
TPR
Renal artery stenosis etc.
Renal ischemia
Kidney
Renin
Angiotensin II
Various renal diseases
Aldosterone
Na+ retention
Functioning renal mass
90% Primary ('essential') hypertension
7% Renal
3% Hormonal and other causes
3 Hormonal hypertension
11-desoxy-corticosterone (DOC)
Mineralo-corticoid effect
Increased catecholamine effect
Therapeutic glucocorticoids
Aldosterone
Cortisol
Catecholamines
4 Other forms of hypertension:
cardiovascular, neurogenic, drugs
Hypophysis
Cortisol deficiency
ACTH
Adrenal cortex
a Adrenogenital syndrome
Adrenal cortical tumor
b Primary hyperaldo-steronism (Conn's s.)
ACTH
or
Adrenal cortical tumor
c Cushing's syndrome
Adrenal medullary tumor
d Pheochromocytoma

Hypertension take home message?

- Salt?
- Electrolytes?
- Kidney?
- Blood vessels?
- Heart?

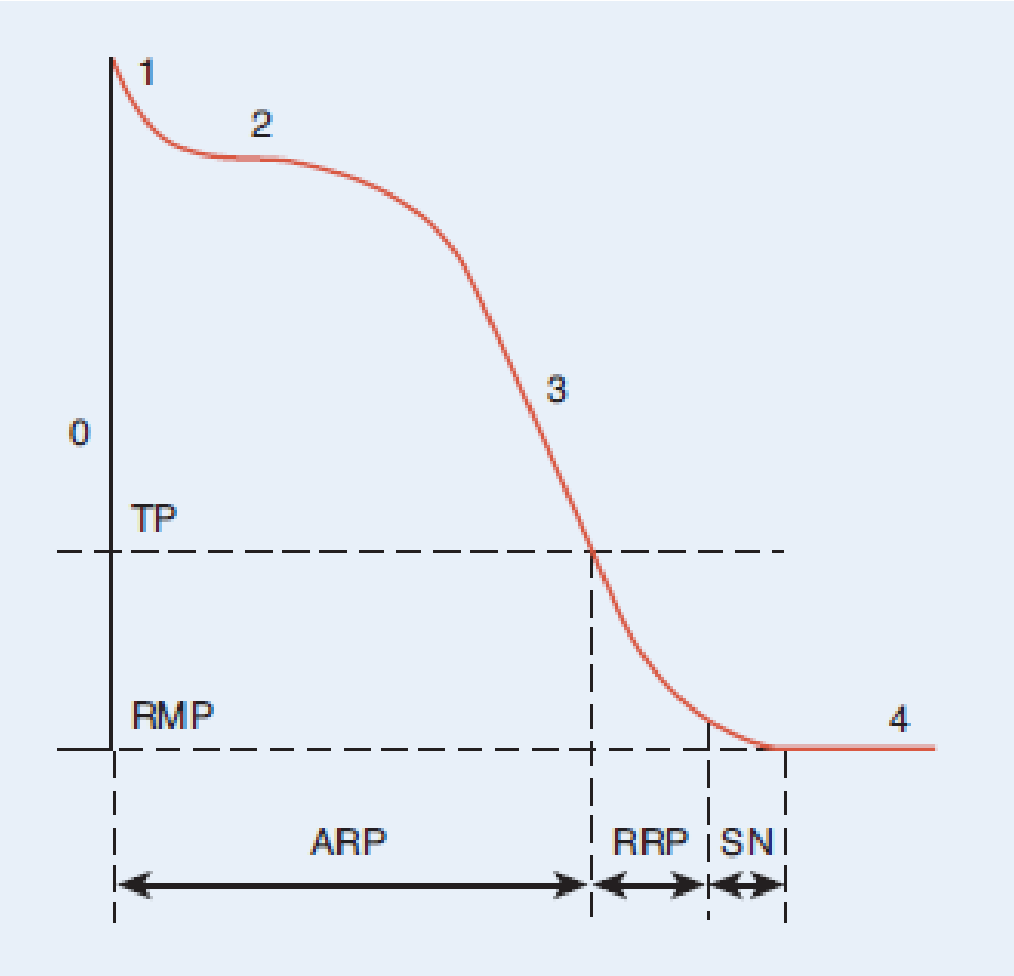
Cardiac disorders

Phases in an action potential recorded from (A) a fast response in a cardiac muscle cell and (B) a slow response recorded in the sinoatrial and atrioventricular nodes. The phases of the action potential are identified by numbers: phase 4, resting membrane potential; phase 0, depolarization; phase 1, brief period of repolarization; phase 2, plateau; phase 3, repolarization. The slow response is characterized by a slow, spontaneous rise in the phase 4 membrane potential to threshold levels; it has a lesser amplitude and shorter duration than the fast response. Increased automaticity (B) occurs when the rate of phase 4 depolarization is increased



Cardiac disorders

Diagram of an action potential of a ventricular muscle cell, showing the threshold potential (TP), resting membrane potential (RMP), absolute refractory period (ARP), relative refractory period (RRP), and supernormal (SN) period.



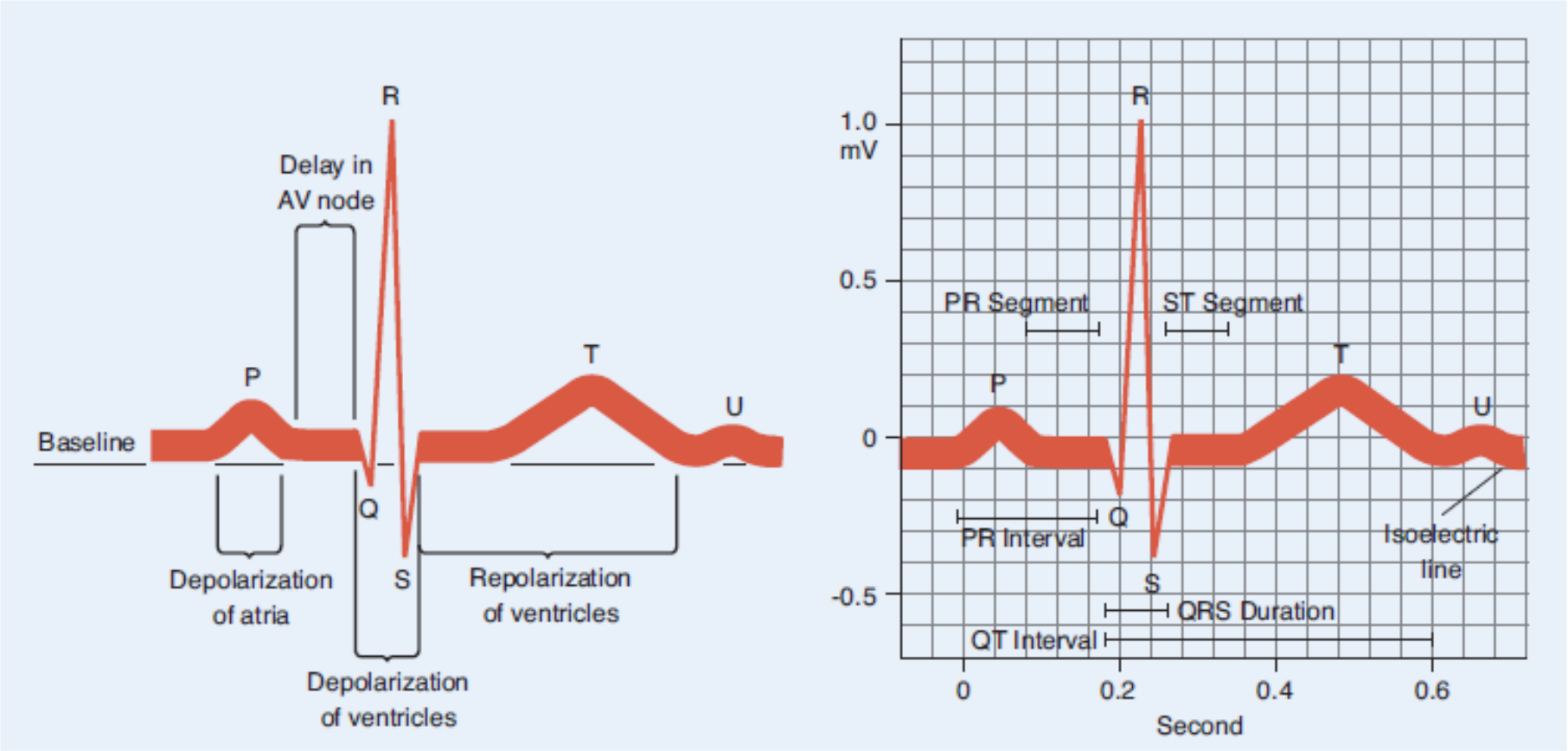


Diagram of the electrocardiogram (lead II) and representative depolarization and repolarization of the atria and ventricles. The P wave represents atrial depolarization, the QRS complex ventricular depolarization, and the T wave ventricular repolarization. Atrial repolarization occurs during ventricular depolarization and is hidden under the QRS complex. AV, atrioventricular.

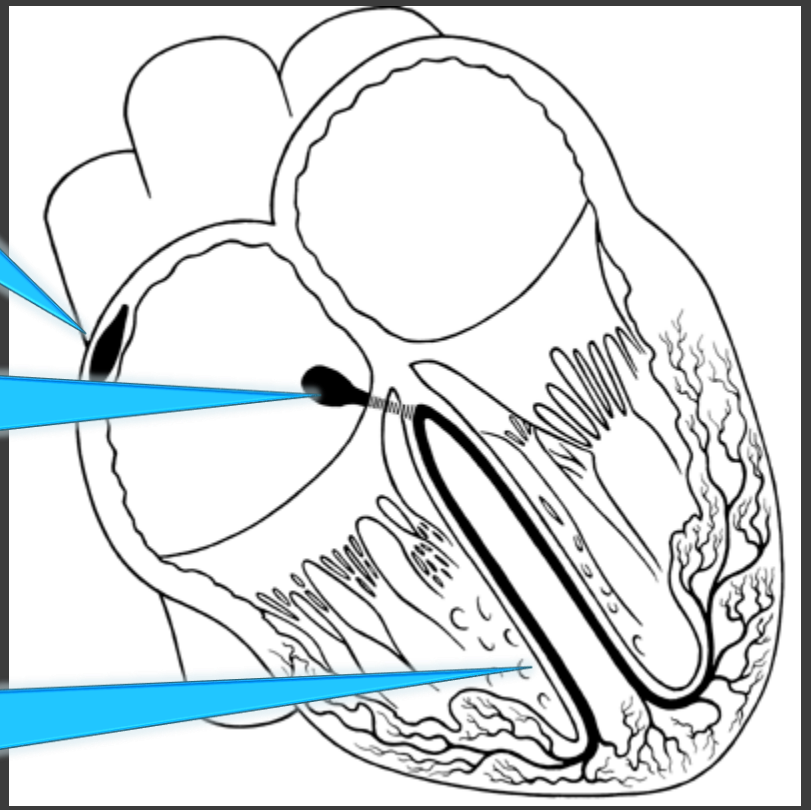
Physiology of the normal heart

Normal conduction pathway:

1- SA node generates action potential and delivers it to the atria and the AV node

2- The AV node delivers the impulse to purkinje fibers

3- purkinje fibers conduct the impulse to the ventricles



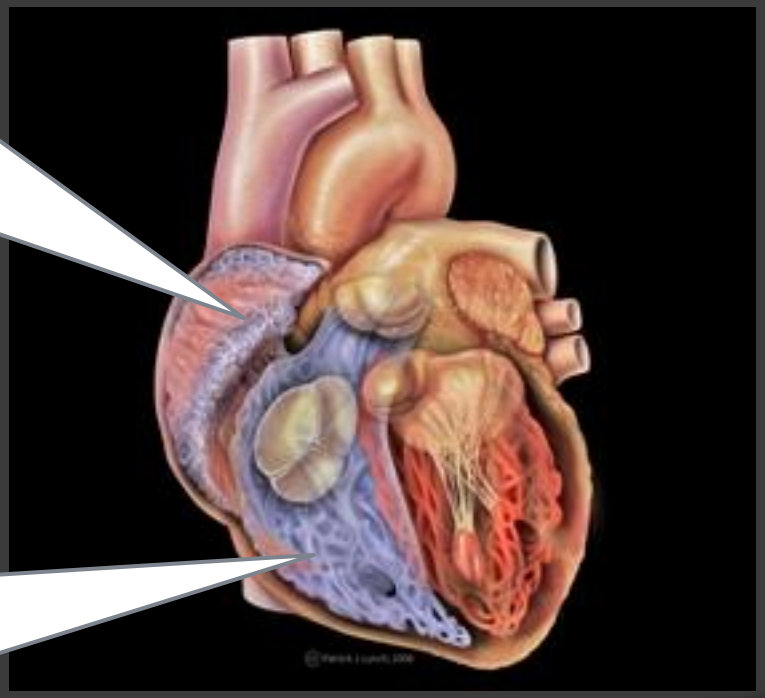
Other types of conduction that occurs <u>between myocardial cells</u>: When a cell is depolarized → adjacent cell depolarizes along

Arrhythmia

Arrhythmia /dysrhythmia: abnormality in the site of origin of impulse, rate, or conduction

1. Bradycardia - Cardiac beats below 60 beats per minute .
2. Tachycardia – Cardiac beat above 100 beats per minute.

If the arrhythmia arises from atria, SA node, or AV node it is called supraventricular arrhythmia



If the arrhythmia arises from the ventricles it is called ventricular arrhythmia

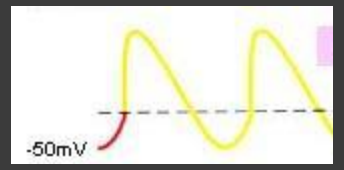
Causes of arrhythmia

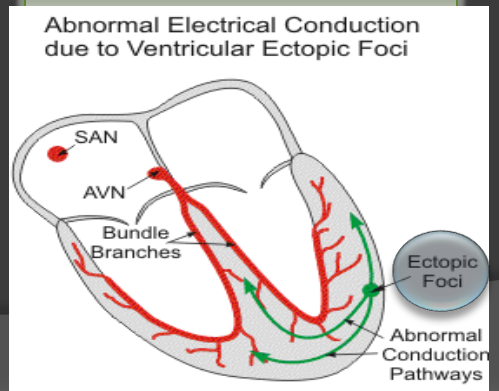
- arteriosclerosis
- Coronary artery spasm
- Heart block
- Myocardial ischemia

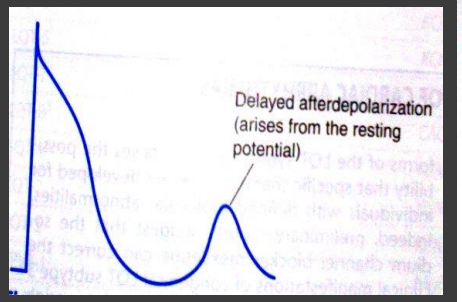
Mechanisms of Arrhythmogenesis

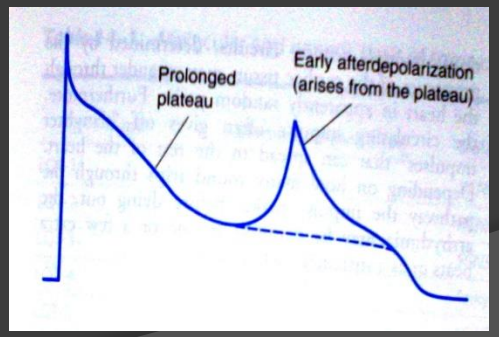
1- Abnormal impulse generation

- Automatic rhythms
  - Enhanced normal automaticity
    - ↑AP from SA node
  - Ectopic focus
    - AP arises from sites other than SA node
- Triggered rhythms
  - Delayed afterdepolarization
  - Early afterdepolarization







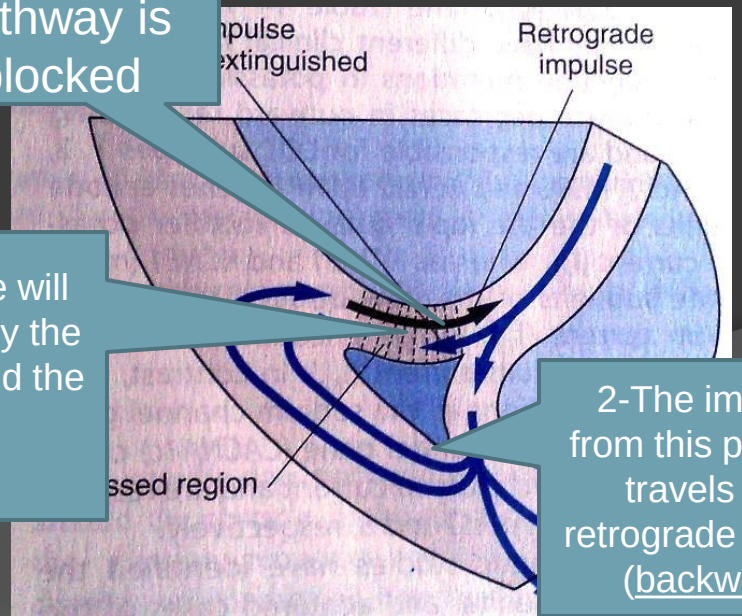


2-Abnormal conduction

- Conduction block
  - 1st degree
  - 2nd degree
  - 3rd degree
- Reentry
  - Circus movement
  - Reflection

This is when the impulse is not conducted from the atria to the ventricles

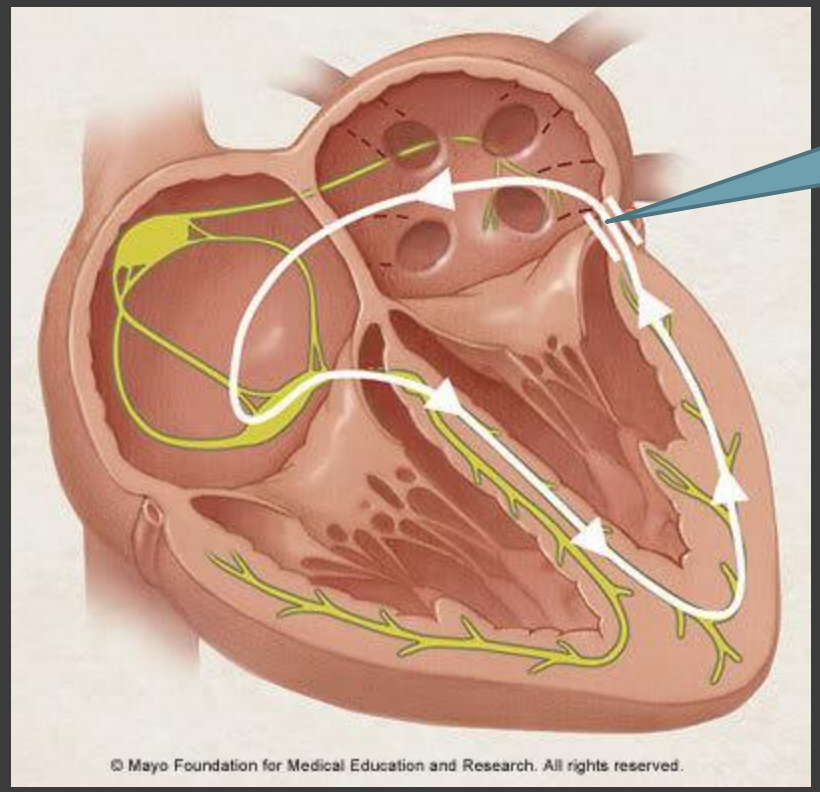
1-This pathway is blocked



3-So the cells here will be reexcited (first by the original pathway and the other from the retrograde)

2-The impulse from this pathway travels in a retrograde fashion (backward)

Abnormal anatomic conduction



Here is an accessory pathway in the heart called Bundle of Kent

- Present only in small populations
- Lead to reexcitation → Wolf-Parkinson-White Syndrome (WPW)

Types of Arrhythmia

Supraventricular Arrhythmias

- ✓ Sinus Tachycardia: high sinus rate of 100-180 beats/min, occurs during exercise or other conditions that lead to increased SA nodal firing rate
- ✓ Atrial Tachycardia: a series of 3 or more consecutive atrial premature beats occurring at a frequency >100/min
- ✓ Paroxysmal Atrial Tachycardia (PAT): tachycardia which begins and ends in acute manner
- ✓ Atrial Flutter: sinus rate of 250-350 beats/min.
- ✓ Atrial Fibrillation: uncoordinated atrial depolarizations.

AV blocks

A conduction block within the AV node , occasionally in the bundle of His, that impairs impulse conduction from the atria to the ventricles.

ventricular Arrhythmias

- **Ventricular Premature Beats (VPBs):** caused by ectopic ventricular foci; characterized by widened QRS.
- **Ventricular Tachycardia (VT):** high ventricular rate caused by abnormal ventricular automaticity or by intraventricular reentry; can be sustained or non-sustained (paroxysmal); characterized by widened QRS; rates of 100 to 200 beats/min; life-threatening.
- **Ventricular Flutter** - ventricular depolarizations >200/min.
- **Ventricular Fibrillation** - uncoordinated ventricular depolarizations

Arrhythmia take home message?

- Bradycardia?
- Tachycardia?
- Conduction velocity?
- Refractory period?