

L3: Control of Blood Flow: Physiology

Circulation	Vasoactive Metabolites	Local or Systemic Control	Mechanical Effects
Coronary	Hypoxia Adenosine	Local control	Coronary vessels mechanically compressed during systole
Cerebral	CO ₂	Local control, no systemic control (BBB)	
Skeletal muscle	Lactate Adenosine K ⁺ CO ₂	Local and systemic (sympathetic control) Local: important during exercise Sympathetic: important during rest -Alpha1 receptors - vasoconstriction -Beta2 receptors - vasodilation	Muscular activity compresses blood vessels
Skin		Sympathetic /systemic control for temperature regulation	

L8: Anti-hypertensives: Pharm and Clinical

Non-pharm interventions

- DASH dietary pattern
- Sodium: <1500 mg/d
- Physical activity:
 - 90-150 min/wk of aerobic exercise at 65-75% of HR
- Alcohol limit to:
 - Men: <=2 drinks daily
 - Women: <= 1 drink daily

Estimated 10-year atherosclerotic cardiovascular disease risk (ASCVD)

- takes into account various factors
- Check if $\geq 10\%$, then prescribe BP-lowering med

Drug decisions:

First-line medications for HTN (no comorbidities)

- thiazide diuretics
- Calcium channel blockers
- ACE inhibitors or ARBs
- NO beta blockers*

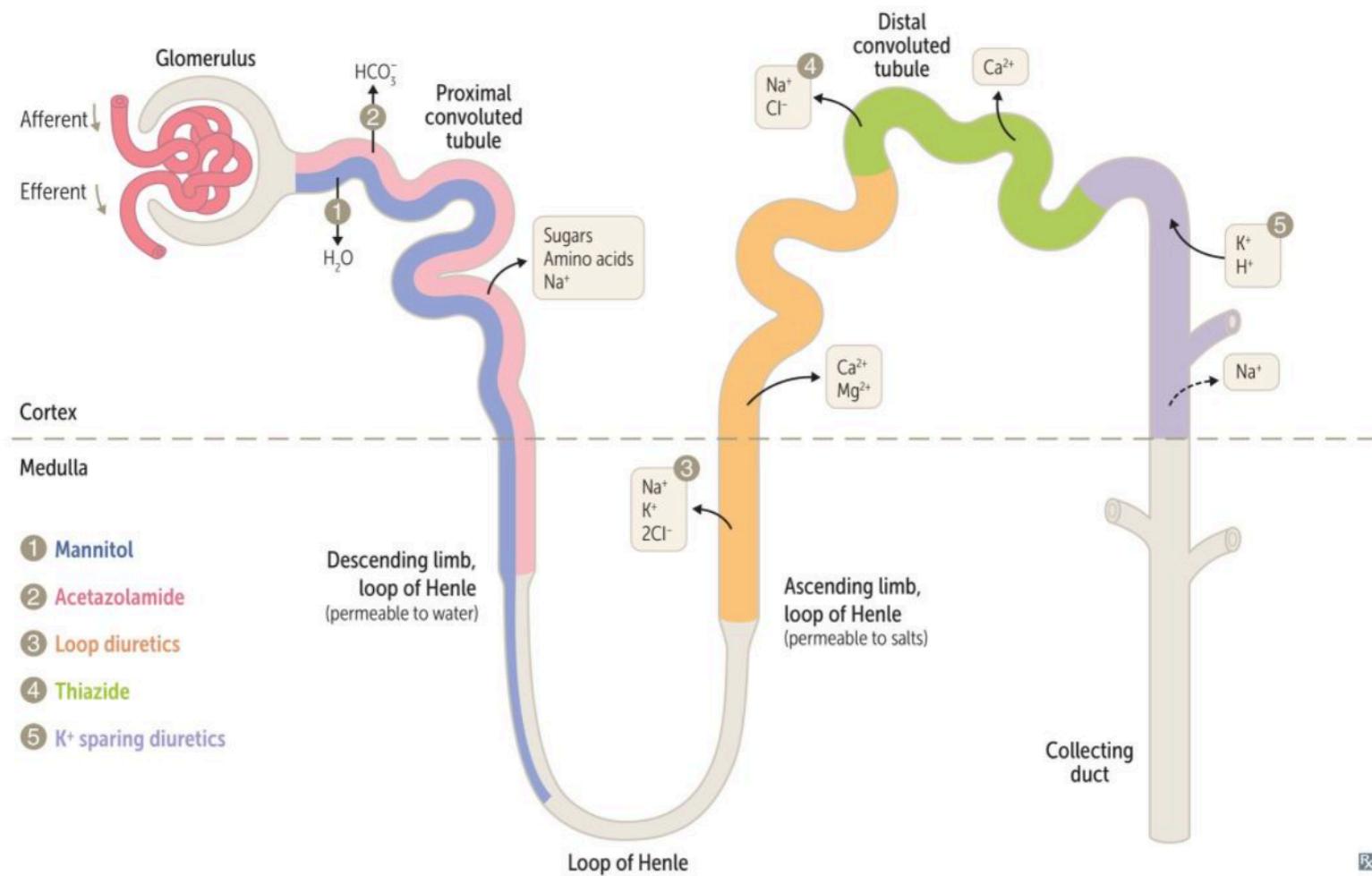
Patients without comorbidities:		<ul style="list-style-type: none">- For stage 1 HTN, start with one agent- For stage 2 HTN, start with two agents
Patients with comorbidities	Stable Ischemic HD	First-line: Beta blockers, ACE inhibitors or ARBs Can add other drugs to further control HTN (dihydropyridine CCBs, thiazide diuretics and/or mineralocorticoid receptor antagonists)
	Heart failure	First-line: Beta blockers, ACE inhibitors or ARBs , diuretics, mineralocorticoids
	Chronic kidney disease	First line: ACE inhibitor If not tolerated: ARB

	Medication class	Medication name	Mechanism	Clinical use	Adverse effects
Diuretics	Diuretic: proximal tubule	Acetazolamide	Decrease stroke volume Carbonic anhydrase inhibitor - inhibits exchange of H+ for Na+ in proximal tubule (inhibit reabsorption of Na+)	Mountain sickness (metabolic alkalosis) Glaucoma	<u>Metabolic acidosis</u>
	Diuretic: loop	Furosemide Bumetanide Torsemide Ethacrynic acid	Inhibit Na+/L+/2 Cl co-transport in ascending loop of Henle	Hypercalcemia (loops lose Ca2+)	Ototoxicity
	Thiazide diuretics	Hydrochlorothiazide Metolazone Indapamide Chlorthalidone	Block Na+/Cl- cotransport at distal tubule	Hypercalciuria	Hyper GLUC (glycemia, lipidemia, uricemia, calcemia)
	K-Sparing diuretics/mineralocorticoid receptor antagonists	Spironolactone	Blocks aldosterone affect at collecting duct → blocks stimulation of Na/K pump Leads to <u>increase in serum K+</u>	Primary hyperaldosteronism (hypokalemia since aldosterone leads to greater K+ secretion) Heart failure	Hyperkalemia Gynecomastia (breast tissue formation)
Beta blockers	Beta 1 blockers	Esmolol Metoprolol	Decreases contractility (inotropy) and HR (chronotropy) Also inhibit beta blockers on juxtaglomerular cells -		Beta blockers commonly cause sedation, fatigue, impotence Worsen heart failure (avoid for)

			inhibit renin release		decompensating HF)
	Non selective beta blocker (beta 1 and 2)	Nadolol Propranolol			Do not give to asthmatic patient (B2 activation necessary for bronchodilation) Severe AE: bronchoconstriction
	Non selective beta blocker + alpha	Carvedilol Labetalol Isoproterenol		Labetalol for pregnancy (preferred over methyldopa)	
	Non-selective beta blocker + sympathomimetic	Acebutolol (beta-1) Penbutolol Pindolol			
CCB	Calcium channel blocker (non dihydropyridines)	Diltiazem Verapamil	Bind to L type Ca channels in myocardium Decrease contractility AND Decrease heart rate		Worsens heart failure Verapamil - constipation
	Dihydropyridine CCB	Amlodipine Nicardipine (IV) Nifedipine (pregnancy)	Binds L type Ca channels in periphery Decreases peripheral vascular resistance (potent vasodilators)		Peripheral edema
RAAS inhibitors	ACE inhibitors	-pril	Targets RAAS system - lowers systemic vascular resistance Blocks ACE enzyme (which converts	Systolic HF (the drug decreases afterload)	Hyperkalemia (blocked action of aldosterone) Cough, angioedema Teratogenic*

			Angiotensinogen I → Angiotensinogen II)		Leads to high bradykinin levels
	Angiotensin II receptor blockers (ARBs)	-artan	Targets RAAS system - lowers systemic vascular resistance		Teratogenic*
Alpha targeting meds	Alpha 1 blockers	Doxazosin Prazosin Terazosin		Benign prostatic hyperplasia	Orthostatic hypotension (lightheaded when standing up)
	Alpha 2 agonist	Methyldopa Clonidine Reserpine		Methyldopa - good for pregnancy	Clonidine - rebound hypertension after sudden withdrawal
Direct vasodilators	Direct vasodilators	Hydralazine		pregnancy	Lupus like syndrome
		Minoxidil			Hypertrichosis
		Sodium nitroprusside		Hypertensive emergencies (like aortic dissection)	Cyanide toxicity (only use short-term)

Diuretics site of action



L9: HTN Pathology

Vascular response to injury:

- Smooth muscle cells migrate from vascular media to intima and secrete ECM
- Expression of procoagulants, adhesion molecules, proinflammatory factors, becomes “sticky”

Arteriolosclerosis

1. Hyaline arteriolosclerosis

- Endothelial injury → leaking of plasma proteins into artery (pink band) and matrix production
- Causes:
 - Aging
 - Diabetes: more generalized hyalinosis than hypertensive
 - Affects both afferent and efferent arterioles in kidney
 - Benign hypertension
 - Affects afferent arterioles of kidney (**hypertensive nephrosclerosis**)

2. Hyperplastic arteriolosclerosis

- Caused by malignant hypertension → proliferation of smooth muscle along intima (onion-skinning)
- Can see fibrinoid necrosis of afferent arteriole of kidney
- Flea-bitten appearance of kidney - petechial hemorrhage/acute renal failure
- Brain:
 - lacunar infarcts
 - hypertensive encephalopathy
- Heart:
 - concentric hypertrophy of LV (lumen reduction, wall thickens)
 - Larger myocytes, NOT more myocytes
 - DNA replication without cell division
 - Fibrosis/ischemia due to increased distance from blood vessels
 - left atrial dilation (due to ventricular stiffness) → atrial fibrillation

Atherosclerosis

Disease of large and medium sized vessels → atherosclerotic plaques form along intima

Pathogenesis

1. Chronic endothelial injury (ex: from smoking, hypertension etc.)
2. Endothelial dysfunction/ response to injury - increased permeability, leukocyte adhesion
3. Macrophage activation, smooth muscle recruitment to intima
4. Macrophages and smooth muscle cells engulf lipid/oxidize LDL (fatty streak formation)
5. Smooth muscle proliferates in intima, ECM deposition, fibrous cap formation

Locations of atherosclerosis

- Often occurs at vessel branch points with flow turbulence
- Coronary arteries involve most mortality → ischemic heart disease/MI

Progression

- > 70% stenosis → end organ damage

L10: Acute Coronary Syndrome

Stable angina:

- > 70% artery blockage → symptoms (exertional chest pain)

Acute coronary syndrome:

1. Unstable angina
 - > 70% blockage + thrombosis with incomplete artery occlusion
2. Myocardial infarction - plaque ruptures → acute thrombosis + cardiac myocyte necrosis
 - Elevated troponin and CK-MB
 - STEMI
 - Transmural infarct (full thickness)
 - ST segment elevation
 - NSTEMI
 - Subendocardial infarct

Therapy for Stable Angina

- Fix coronary flow (Stent)
- Meds:
 - Aspirin - antiplatelet
 - Nitrates - venodilation to decrease venous return to heart
 - Beta blockers and CCB: decrease HR and BP, contractility
 - Ranolazine

Therapy for Acute Coronary Syndrome (Unstable angina, STEMI, NSTEMI)

- Immediate → MONA: morphine, oxygen, nitroglycerin, aspirin and/or clopidogrel (ADP inhibitor, anti-clotting)
- Thrombolytic therapy (alteplase)
- Can give oral beta blockers (reduce myocardial demand, treat arrhythmias)
- Secondary prevention
 - Aspirin - for life
 - Statin
 - ACE inhibitors - decrease afterload and blood volume
 - Smoking cessation

Vasospastic angina

- Coronary artery spasm
- Triggered by excess vagal tone (at night)
- Acetylcholine makes it worse - triggers vasoconstriction because of nitric oxide deficiency

L11: Ischemic Heart Disease Pathology

Ischemic heart disease: due to imbalance between supply and demand for oxygenated blood in the heart

Pathogenesis of ischemic heart disease:

- What determines demand:
 - HR, workload, hypertrophy
- What determines supply:
 - Obstruction to flow (atherosclerosis, embolism, dissection etc.)

- Decreased O₂ carrying capacity of blood (anemia, carbon monoxide)
- Decreased perfusion from hypotension/shock

Progression of injury:

- Subendocardial infarction
 - Transient obstruction - regional
 - Global hypotension - circumferential
 - Small intramural vessel occlusions - microinfarcts
- Transmural infarction
 - Permanent occlusion of left anterior descending artery
 - Permanent occlusion of left circumflex branch
 - Permanent occlusion of right coronary artery (posterior descending branch)

Time from infarction	Gross changes	Microscopic changes	Complications
< 4 hours	none	none	Cardiogenic shock (massive infarction, loss of blood supply to vital organs), congestive heart failure (blood backs up and not pumped forward), arrhythmia
4-24 hours	Dark discoloration	Coagulative necrosis (loss of nuclei)	Arrhythmia (if you damaged conducting cells)
1-3 days	Yellow pallor	Neutrophils	Fibrinous pericarditis (with transmural infarction) → inflammatory debris enters pericardium
4-7 days	Yellow pallor	Macrophages	Wall thins from macrophage eating necrotic debris: Rupture of ventricular free wall (tamponade), interventricular septum (shunt) or papillary muscle (mitral insufficiency)

1-3 weeks	Red border emerges at edge of infarct from granulation tissue	Granulation tissue with fibroblasts, collages, blood vessels	
Months	White scar	Fibrosis	Ventricular aneurysm

Macroscopic Pathology of MI

- 0-4 hours: nothing
 - Ischemic myocardium stains white with tetrazolium salts, healthy tissue stains red (post-mortem in person who died of MI in 2-3 hours)
- 4-24 hours: dark mottling +/-
 - Coagulative necrosis
- 3-7 days: central tan yellow softening, hyperemic border (more blood)
- 7-10 days: maximally yellow tan and soft with depressed red tan borders
- 10-14 days: red-gray depressed infarct borders
- >2 months: scarring causes wall thinning, can see compensatory hypertrophy

Microscopic Pathology of MI

- Within minutes of ischemia:
 - Myofibrillar relaxation
 - Glycogen depletion
 - Cell and mitochondrial swelling
 - Reversible
- Severe ischemia for >20-30 minutes - irreversible damage
 - Necrosis of cardiac myocytes (loss of nucleus) - coagulative necrosis
 - Intracellular macromolecules leak out of cells
- Timeline
 - < 4 hrs: no microscopic changes
 - 4-12 hrs: beginning coagulative necrosis (removal of nucleus)
 - 12-24 hrs: early neutrophilic infiltrate
 - 1-3 days: brisk neutrophilic infiltrate, loss of nuclei
 - 3-7 days: dead myofibers are phagocytosed by macrophages at edges of infarct
 - 7-10 days: macrophages increase, peripheral granulation tissue
 - 10-14 days: increasing granulation tissue
 - 2-8 weeks: decreasing cellularity, increasing collagen
 - >8 weeks: collagenous scar

1 day: coagulative necrosis

Inflammation (neutrophils → macrophages)

1 week

Granulation tissue

1 month: scar

Reperfusion injury:

- Necrosis with contraction bands - hypercontraction? due to Ca⁺ influx
- Oxygen influx leads to free radical formation
- Leukocyte aggregation

Complications of MI:

- Dysrhythmia
- Dysfunction of pump as a whole
- Dysfunction of papillary muscles
- Dilation of area of infarction
- Right ventricular dysfunction and RV failure
 - Due to blocked right coronary artery
- Rupture
- Thrombus formation in ventricle
- Ventricular aneurysm

L12: Antianginal Meds

Nitrates

- Vasodilators
 - Veins >> large arteries >> arterioles (varies by dose)
 - Venous dilation is predominant at lower dose → decrease in preload (1)
 - Dilation of arterioles at higher doses → decreases afterload (2)
 - Together these decrease myocardial oxygen demand
- Increase intracellular cGMP (3) → stimulates protein kinase → activates myosin light chain phosphatase → smooth muscle relaxation
 - Some smooth muscle relaxation of coronary arteries (least effect)
- Examples: nitroglycerin, amyl nitrate, sodium nitroprusside (used for HTN emergencies, not angina)

- Side effects:
 - Postural/orthostatic hypotension
 - Reflex tachycardia
 - Headache
 - Skin flushing
 - Methemoglobinemia (rare)
 - Contraindicated in patients taking Viagra
- Clinical uses: typical angina, prinzmetal's angina, emergencies, maintenance therapies
- Can develop tolerance if given too often

Beta blockers:

- Mechanism: Decrease HR and myocardial contractility
 - Beta 1 antagonists - effects on heart tissue
- Relieves angina (reduces workload of the heart)
- Side effects:
 - Bradycardia and decreased contractility - bad for decompensating HF (fluid overload)
 - Fatigue, sexual dysfunction
 - Propranolol and metoprolol - lipophilic - cross BBB → lethargy and depression
 - Nonselective beta blockers:
 - Can block beta-2 receptors in coronary artery → lead to vasoconstriction because of unopposed alpha
 - Bronchoconstriction also caused
 - Do NOT use in Prinzmetal angina (non-selectives will worsen spasm of coronary arteries)
- Clinical use:
 - Combo therapy with nitrates to prevent angina (prevent reflex tachycardia caused by nitrates)

Calcium channel blockers

- Clinical use: prolong time to onset of angina, can be used in combo with beta blockers and nitrates
 - First line treatment for prinzmetal angina
- Can cause coronary vasodilation → relieves angina (dihydropyridine CCB)

Ranolazine

- Mechanism: inhibition of late sodium current in ventricular muscle, improves relaxation of heart
- Ischemia leads to activation of late Na⁺ current → increase intracellular Na⁺ → Ca²⁺ pump switched to influx mode → increase in intracellular Ca²⁺ → causes sustained depolarization in AP → increased muscle tension and ischemia
- May cause QT prolongation

L13: Blood Vessels Pathology

Vascular Tumors and Tumor-Like Conditions

Benign vascular ectasias (**non-neoplastic**)

- Dilation of pre-existing small vessels
- Nevus flammeus and port wine stain are birthmarks
- Spider telangiectasias
 - Pulsatile, blanch with pressure
 - Associated with hyperestrogenemia (ex: pregnancy), liver cirrhosis
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu Disease)
 - Autosomal dominant, mutations in TFG-beta
 - Bleeding is complication

Hemangioma

- Benign **neoplastic** proliferation of endothelial cells
- Capillary: most common type
 - Pyogenic granuloma: capillary hemangioma growing as mass on mucosal tissue - resembles but is not a granuloma
- Cavernous hemangioma: larger vessels, more infiltrative
- Glomus tumor
 - Painful tumor under fingernails

Other diseases:

- Bacillary angiomatosis
 - Caused by bartonella/ cat-scratch disease
 - Frequently in AIDS patients
- "Congenital" berry aneurysms
 - Most commonly occurs in circle of Willis
 - Most common cause of spontaneous subarachnoid hemorrhage (in brain)
 - Aneurysms commonly occur at branch points
 - Cause can be genetic (ex: CTD, family hx)
- Fibromuscular dysplasia
 - Abnormal growth of walls in medium and large muscular arteries (ex: renal)

- Common cause of renal artery stenosis (10-20%), in females <50 → secondary hypertension
- String of beads appearance

Diseases of Aorta

Aneurysm

- Types:
 - True aneurysm: involves all 3 layers of artery
 - Pseudoaneurysm: wall defect
 - Communicating extravascular hematoma (localized collection of blood outside vessel)
- **Abdominal aortic aneurysm**
 - Common in men, smokers, usually asymptomatic
 - Pathogenesis: atherosclerosis → degeneration of media
 - Typically occurs below renal arteries and above aortic bifurcation (infrarenal)
 - Complications:
 - Obstruction of aortic branches
 - Embolism
 - rupture* - chance of rupture depends on size
- **Thoracic aortic aneurysm**
 - Causes: HTN, CTD (Marfan's, Ehlers Danlos), infections (**syphilitic** end arteritis)
 - Marfan syndrome:
 - Autosomal dominant
 - Defect in Fibrillin-1 → increased TGF-beta signaling
 - Clinical features: tall, long fingers etc.
 - CVD issues: mitral valve prolapse (chordae tendinae rupture), aortic aneurysm and dissection
 - Micro: **cystic medial**/elastic lamellar degeneration of aorta
 - Complications
 - Dilatation of aortic valve root → aortic insufficiency
 - Compression of mediastinal structures
 - Thrombosis/ embolism / rupture

Aortic Dissection

- Formation of blood-filled channel within aortic wall (media)
 - Intimal tear → blood flowing within media
- Pathogenesis: HTN, CTD → weakness of aortic media

- Blood flows between inner ⅓ and outer ⅔ of media of aorta (where vasa vasorum come in)
- Usually occurs in proximal 10 cm. of aorta
- Classification:
 - Proximal (type A): ascending aorta +/- descending
 - Requires surgical tx
 - Distal (type B): beyond subclavian artery
 - Medical tx
- Complication:
 - Rupture into body cavity like pericardium - tamponade - common cause of death
- Sx: sharp tearing chest pain, radiates to the back

Aortitis (large vessel vasculitis)

- Giant cell arteritis:
 - Path: Chronic **granulomatous** inflammation affecting large to medium vessels → medial degeneration, intimal thickening
 - Associated with HLA-DR4
 - Self-limited course BUT dangerous due to possible blindness
 - Occurs in carotid, aorta
- Takayasu arteritis
 - Path: marked vascular thickening with luminal reduction, obstructions of arteries
 - Micro: early adventitial inflammation → medial inflammation with **giant cells** → healing with fibrosis and **intimal thickening**
(May be indistinguishable from giant cell arteritis)
 - Asian women, associated with HLA-B52
 - Chronic course
 - Occurs in aorta and branches

L14: Hyperlipidemia

Framingham heart study – lead to first paradigm shift from treatment to prevention

- But has limits (not diverse study subjects), underestimation in young people

Dyslipidemia in type 2 diabetes

- Elevated triglycerides
- LDL elevated, reduced HDL

Metabolic syndrome

- Distinctive body type with increased abdominal circumference
- Diagnosis (3 of below criteria)
 - Waist circumference
 - High triglycerides
 - Low HDL
 - High BP
 - High fasting glucose
- Has increase risk of CV death

Statins:

- Lower LDL C
- Lower triglyceride
- Raise HDL
- Other mechanisms: better endothelial function, reduced inflammation, reduced coagulation

Recommendations:

1. Lifestyle recommendation
2. High **statin** dose
3. High-risk ASCVD → LDL cholesterol has not reached **70 mg/dl** with **statins** → addition of nonstatins
 - a. **Ezetimibe**
 - b. **PCSK9 inhibitor**
4. Severe primary hypercholesterolemia → begin statin right away
 - a. If LDL remains above 100, add ezetimibe
 - b. And then if still high, add PCSK9
5. Younger people with diabetes → start moderate dose statin therapy

L15: Hyperlipidemia Therapeutics

Familial dyslipidemias:

- Type I - Hyperchylomicronemia
 - Elevated triglycerides due to deficiency in degrading enzyme
 - Clinical: pancreatitis, pruritic xanthomas
 - NO increased risk of CAD

- Type IIb - familial combined hypercholesterolemia
 - Elevated cholesterol
 - Increased risk of CAD (early!)
 - Clinical: tendon xanthomas, corneal arcus
- Type IIa - familial hypercholesterolemia
 - Extremely high LDL levels - low LDL receptors
 - Premature CAD
 - Clinical: palmar xanthomas
- Type IV: Hypertriglyceridemia
 - Overproduction of VLDL - elevated triglycerides
 - Clinical: pancreatitis

Drug	Mechanism	Clinical Uses	Adverse Effects
Statin	<p>Inhibits HMG-CoA reductase → reduced hepatic cholesterol and increased LDL receptor expression → increases LDL clearance</p> <p>Metabolized by CYP except for pravastatin</p>	<p>Atorvastatin and rosuvastatin - more potent</p> <p>Pravastatin and simvastatin - less potent but less AE</p> <p>Statins very good at lowering LDL cholesterol, moderate at decreasing triglycerides, bad at increasing HDL</p>	<p>Rare - hepatotoxicity</p> <p>Myopathy</p> <ul style="list-style-type: none"> - Risk increased when given with fibrates or nicotinic acid <p>Contraindicated in pregnancy, nursing mothers, young children</p> <p>Metabolized by CYP:</p> <p>Drugs that inhibit statin metabolism - cyclosporine, metronidazole</p> <p>Drugs that increase statin metabolism - rifampin, phenytoin</p>
Ezetimibe	Inhibits luminal cholesterol uptake by enterocytes	Additive with statins	
Evolocumab and Alirocumab	PCSK9 inhibitor (immunotherapy)	Additive with statins and ezetimibe	

	<p>Antibodies that bind to PCSK9</p> <p>PCSK9 normally binds LDLR and stimulates receptor endocytosis</p> <p>Inhibiting PCSK9 leads to more LDLR on surface → more LDL brought in to liver</p>		
Cholestyramine, colestipol, colesevelam	Bile acid sequestrants - positively charged binding resins that ionically bind bile acids → excreted in feces		<p>Resins have sand consistency</p> <p>Bloating, flatulence, constipation</p> <p>Can cause increase in serum triglycerides</p> <p>Can bind other drugs (anions)</p>
Niacin	<p>Inhibits lipolysis</p> <p>Also reduces VLDL synthesis in hepatocyte</p> <p>ALSO decreases clearance of HDL (<u>increasing HDL levels</u>)</p>	Used less now due to many AEs	<p>Intense flushing and pruritus</p> <p>GI effects</p> <p>Increases plasma glucose (don't give diabetics) and uric acid</p> <p>Hepatotoxicity</p> <p>Myositis risk if used in statin</p>
Fenofibrate, Gemfibrozil	<p>Fibrates</p> <p>Up-regulate lipoprotein lipase → increase clearance of VLDL and increased oxidation of fatty acids in muscle (decreases triglycerides)</p>	Not much clinical outcome data (don't use unless intolerant to other meds) - use for <u>high triglycerides</u>	<p>Myopathy when given with statins</p> <p>Cholelithiasis - gallstones</p> <p>Potentiates warfarin action</p>

L19: CHF Pathology

Heart failure

- Occurs when heart output cannot meet the metabolic needs of the body
- Causes:
 - Pump failure (systolic or diastolic)
 - Systolic failure: inability of heart to pump blood
 - Ischemic heart disease or HTN or **cardiomyopathy**
 - Diastolic failure: inability of heart to completely relax and fill
 - HF with preserved ejection fraction
 - Common in older people with stiff heart
 - Obstruction to flow
 - Aortic stenosis/HTN
 - Regurgitant flow
 - Incompetent valves
 - Shunted flow
 - Ventricular/atrial septal defect
 - Disorders of electrical conduction (dysrhythmias)
 - Rupture of heart or vessels

How does the heart compensate for heart failure?

- Cardiac dilation
- Neurohumoral compensation
 - Increased heart rate, contractility, vascular resistance
- Structural changes in myocardium: **hypertrophy**
 - Assembly of new **sarcomeres**
 - Increased thickness of myocytes (pressure overload sarcomeres added parallel to long axis)
 - Concentric myocardial hypertrophy
 - Increased length of myocytes (volume overload sarcomeres are added in series)
 - Eccentric myocardial hypertrophy

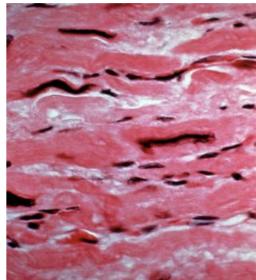
Consequences of heart failure

- **Left heart failure**
 - Diminished systemic perfusion → renal injury, ischemic injury to other organs
 - May present with orthopnea, paroxysmal nocturnal dyspnea

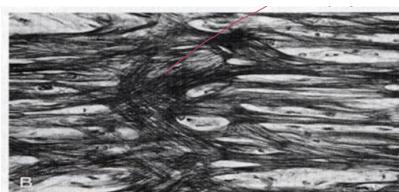
- Increased **pulmonary pressure**, congestion, edema
 - Path of pulmonary edema: increased lung weight, frothy fluid exudes from airways
 - Micro:
 - congested alveolar capillaries
 - pink fluid within alveoli
 - microhemorrhages
 - capillaries rupture and blood leaks into alveoli → **hemosiderin laden macrophages** (blood eating macrophages)
 - Tx: ACE inhibitor
- **Right heart failure**
 - Usually consequence of left heart failure
 - Rarely isolated (cor pulmonale), due to chronic lung disease (hypoxia causes lung vessels to constrict so right heart works harder)
 - Engorgement of systemic venous circulation
 - Hepatosplenomegaly
 - Hepatic congestion - congested central veins → “nutmeg liver”
 - Ascites (build up of fluid in abdomen)
 - Peripheral edema

Cardiomyopathy

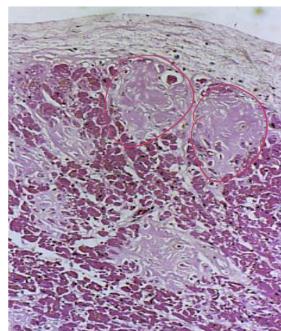
- Dilated (90%)
 - Causes: commonly genetic (**Titin** mutations, ninja star appearing nuclei)
 - Note: can also be caused by Chagas (localized apical wall thinning), alcohol use
 - Dilation of all 4 chambers of heart → systolic dysfunction → biventricular CHF
 - Complications: mitral and tricuspid valve regurgitation, arrhythmias (Pathoma)
 - Mural thrombi
 - Morphology:
 - Increased heart weight
 - Size of ventricular chamber is increased
 - Variable wall thickness
 - Path: Marked **variation** in myocyte size - some hypertrophied and some atrophic



- Hypertrophic
 - Massive myocardial hypertrophy (increased cell size) of left ventricle due to genetic mutation
 - Path: **myocyte disarray**

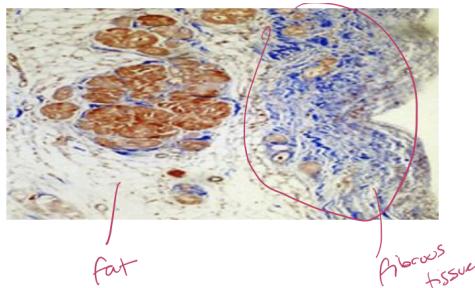


- Cause: genetic mutation of **sarcomere** (AD)
- Heart can't fill b/c of thick muscle → diastolic dysfunction → decreased cardiac output
- May see outflow tract obstruction - mural thickening (blood vessel thickening)
- Restrictive
 - Restriction to filling in diastole
 - Due to infiltrates in wall
 - Cardiac amyloidosis - deposition of protein/hyaline in extracellular heart wall (surrounding myocytes)

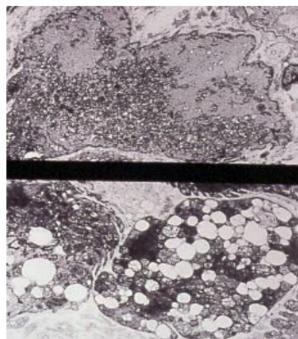


- Proteins include light chains, transthyretin

- Heart wall appears waxy
- Amyloid has green birefringence under polarized light
- Arrhythmogenic cardiomyopathy
 - Familial disease (AD mutations in desmosomal proteins) - **fibrofatty** replacement of right ventricular wall



- Arrhythmias and sudden cardiac death are common
- Peripartum cardiomyopathy
 - Rare disease of late pregnancy
 - Risk factors: increased maternal age, twinning
- Cardiotoxic cardiomyopathy
 - Ex: Adriamycin (doxorubicin) toxicity
 - Path: cytoplasmic **vacuolization** and **lysis** of myofibrils



- Iron overload heart disease
 - Usually causes dilated cardiomyopathy, less frequently restrictive
 - Iron accumulation in myocytes → free radical production

Myocarditis

- Causes: think viruses and drugs
 - Viral: coxsackie virus and enterovirus
 - Non-viral: chagas disease, sarcoidosis, giant cell myocarditis
 - Drugs: adverse response to immune checkpoint inhibitor (rare)
- Path: lymphocyte infiltrates in myocardium → cause myocyte injury
- Dilated cardiomyopathy is possible late complication

Statins - competitive inhibitors of HMG-CoA reductase

L20 & 21: CHF

Heart failure meds

- Top line meds for heart failure with reduced EF (systolic HF)
 - ARNI (entresto)
 - ACEI/ARB
 - Evidence based beta blockers
 - Diuretics
 - Aldosterone antagonists - warning: hyperkalemia
 - SGLT2 inhibitor (**Dapagliflozin**)
 - inhibit glucose and sodium reabsorption
 - Help treat both diabetes and heart failure
 - Hydralazine + isosorbide dinitrate (Bidel)
 - Vasodilation
- Meds for heart failure with preserved EF (diastolic HF) - newer and fewer
 - **Diuretics** as needed
 - SGLT2
 - ARNI
 - MRA (aldosterone inhibitor)
 - ARB

-Digoxin is a second-line drug used to treat severe systolic heart failure. It works by blocking Na⁺/K⁺-ATPase, which leads to increased intracellular calcium → increased contractility

Devices in Heart Failure

- Biventricular pacing
 - Many systolic HF patients have ventricular dyssynchrony → especially with left bundle branch block (LBBB)
 - Depolarization goes down right side but not left → when LV is contracting, septum has already started relaxing (was already depolarized) → sloshing motion in LV → less ejection through aortic valve
 - Tx: cardiac resynchronization therapy
- Treating arrhythmias
 - Implantable cardioverter defibrillator
- Replacement therapy
 - Left ventricular assist device (LVAD) for end stage HF
 - Newer micro-pump

L22: Pericardial Disease and Right Heart Function

Pericarditis

- Inflammation of pericardium
- Most common disease of pericardium
- Clinical features (diagnosis based on 2 of the following 4)
 - Sharp chest pain - worse with a deep breath
 - Fever, leukocytosis (inflammation)
 - Pericardial friction rub
 - New widespread ST elevation or PR depression on ECG
 - T wave inversion in stage 3 pericarditis
 - Pericardial effusion
- Etiology
 - Infectious (coxsackie virus etc.)
 - Autoimmune diseases - common
 - Trauma
 - Drug related (rare) - ex: doxorubicin
- Treatment
 - Anti-inflammatory meds: aspirin, ibuprofen, colchicine

Pericardial effusion / cardiac tamponade

- Can develop from any condition that affects pericardium
- Can lead to cardiac tamponade → lower cardiac output
- Impairs cardiac filling throughout diastole
- Clinical presentation (cardiac tamponade):
 - **Beck's triad**
 - Hypotension
 - Distended jugular veins
 - Muffled heart sounds
 - Pulsus paradoxus
 - Inspiratory fall in systolic BP of greater than 10 mm Hg
 - Inspiration → greater venous return → increased RV size → septum bulges into LV → decreased LV size → decreased cardiac output (this reduction in pressure is exaggerated in tamponade since the RV cannot expand outward)
 - Mitral valve shows less filling, tricuspid valve fills normally (SVC and IVC are outside thorax)
 - Left-right discordance
 - Atrial pressure waveform: **Blunted “y” descent**
 - Y descent is emptying of atrium
 - Blood does not move quickly from atrium to ventricles b/c ventricle is compressed
- EKG: low voltage, **electrical alternans** (heart is swinging)
- CXR: enlarged cardiac silhouette

Pericardial constriction

- Progression from pericarditis
- Involves pericardial inflammation, thickening, +/- calcification
- Clinical presentation:
 - High right atrial pressure
 - Peripheral edema
 - Signs:
 - Elevated JVP**
 - **Pericardial knock** - high-pitched sound during ventricular diastole
 - **Kussmaul's sign** - JVP rises inside of falling during inspiration (anything that impairs right ventricular filling)
 - NO Kussmaul sign in tamponade b/c the pressure can still transmit (fluid!)
 - NO pulsus paradoxus
- Hemodynamics
 - Equalization of diastolic pressures (of all 4 chambers)

- Square root sign (RV pressure)
- **Rapid y descent** (atria pressure) → ventricular filling abruptly terminates (b/c max pressure is hit)
- Treatment
 - Anti-inflammatory
 - If permanent - pericardectomy

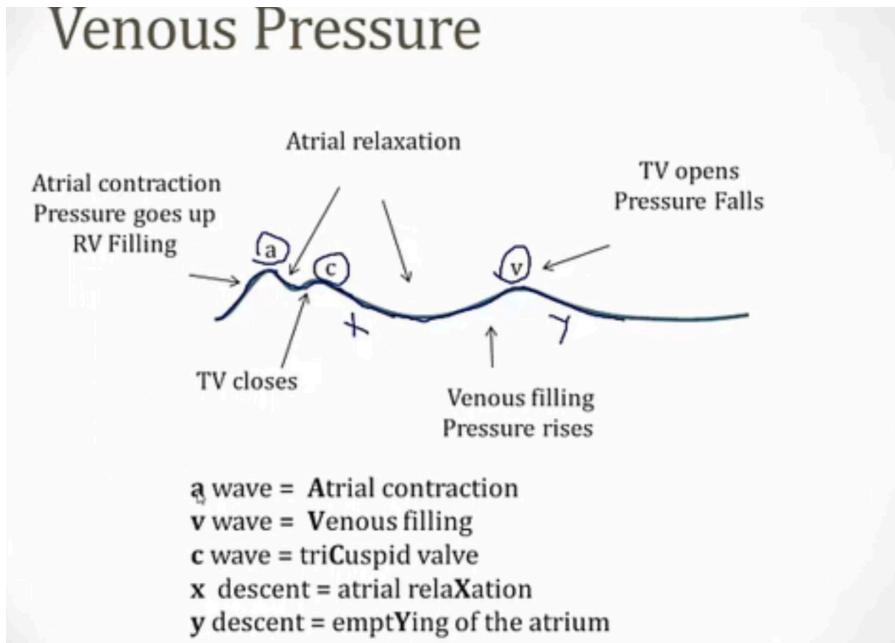
Acute Pulmonary Embolism

- Blockage of pulmonary artery → leads to RV dysfunction
- Diagnosis:
 - **Ventilation perfusion mismatch** (imaging)
 - Serum fibrin **D-dimer** level elevated
 - Lower limb ultrasound
- Pathophysiology
 - PE in pulmonary artery → RV dysfunction
- Causes:
 - Cancer, contraception, etc.
- Diagnosis:
 - RV/LV ratio is high
- Treatment:
 - Thrombolytics, thrombolectomy

Pulmonary hypertension

- Diagnosis:
 - mPAP > 20 mm Hg at rest
- Pulmonary arterial hypertension - subgroup of PH - progressive disease in **small pulmonary arteries** (increased vascular narrowing)
 - Pulmonary vascular resistance > 2 wood units
 - Causes: heritable, connective tissue disease (lupus etc.)
 - Causes **RV failure** (can cause death)
 - Treatments target neurohormonal cascade (like in HF)
 - Endothelin receptor antagonists
 - Exogenous nitric oxide
- Pulmonary venous hypertension - left heart disease
 - Ultimately cause elevated pressure on arterial side of lungs too
- Pulmonary HTN associated with chronic lung disease

Venous Pressure



L23: Exercise

Orthostatic hypotension

- Systolic BP decreases by 20 mm Hg
- Diastolic BP decreases by 10 mm Hg
- Heart rate increases by 20 bpm

What happens during exercise?

- Redistribution of blood flow to different tissues

- Blood flow to skeletal muscle, heart increase
- Sympathetic signaling increases
 - First stroke volume increases but will max out in beginning of exercise
 - As you approach max exercise, HR becomes driver of increased CO
- Blood plasma volume decreases due to prolonged exercise
 - Water leaves blood vessel into interstitial space
 - Greater concentration of Hgb (due to decreased plasma volume)

Dynamic exercise cessation

- Withdrawal of sympathetic tone and return of parasympathetic tone
- Systolic BP falls for up to 12 hours (vasodilation in skeletal muscle persists)

Goal HR of exercise stress test = 85% of maximum predicted HR

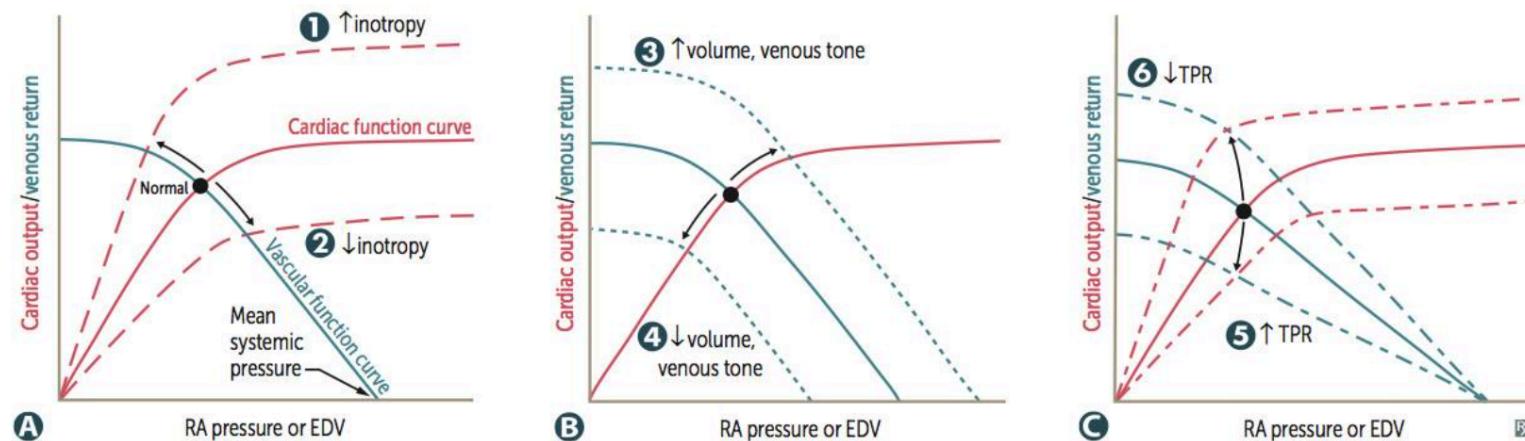
Cardiac output normal = 5 L per min

Steady state HR = if intensity of exercise remains constant, heart rate will level off at a rate

Oxygen dissociation curve

- Right shift - during exercise (more oxygen dissociates - less affinity of Hgb for oxygen)
 - High temperature
 - High CO₂
 - High 2,3-BPG
 - Acidic (lactic acid production during exercise)
- Left shift (Left is Lose - less oxygen dissociates)
 - Low temperature
 - Low CO₂
 - Low 2,3-BPG
 - Basic

Cardiac and vascular function curves



Intersection of curves = operating point of heart (ie, venous return and CO are equal).

GRAPH	EFFECT	EXAMPLES
A Inotropy	Changes in contractility → altered CO for a given RA pressure (preload).	① Catecholamines, digoxin +, exercise ② HF with reduced EF, narcotic overdose, sympathetic inhibition -
B Venous return	Changes in circulating volume or venous tone → altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.	③ Fluid infusion, sympathetic activity + ④ Acute hemorrhage, spinal anesthesia -
C Total peripheral resistance	At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR → altered CO.	⑤ Vasopressors + ⑥ Exercise, AV shunt -

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).