ARTERIOSCLEROSIS AND ISCHEMIC HEART DISEASE

Kenneth Alonso, MD

Framingham Heart Study

- Predictors of subsequent cardiac events and angiographically demonstrated coronary artery disease:
- Advancing age
- The absence of protective female hormones
- Hypertension
- Dyslipidemias
- Diabetes
- Cigarette smoking
- Family history
- Coronary artery Calcium density

Vascular injury and repair

- Associated with endothelial cell dysfunction or loss
- Stimulates smooth muscle cell recruitment and proliferation and associated matrix synthesis
- Neo-intimal smooth muscle cells are motile, undergo cell division, and acquire new biosynthetic capabilities.
- Regulated by local growth factor and cytokine secretion of inflammatory cells
- Results in intimal thickening.
- Fibromuscular hyperplasia is a developmental defect.

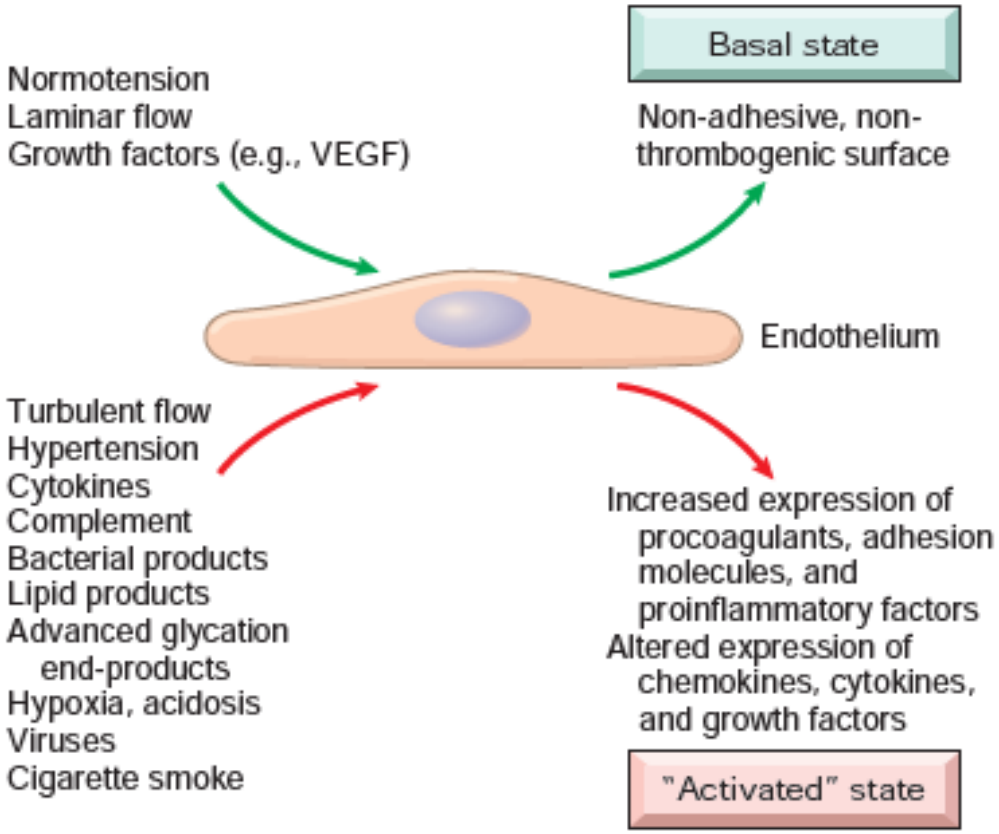


Figure 11-2 Basal and activated endothelial cell states. Normal blood pressure, laminar flow, and low growth factor levels promote a basal endothelial cell state that maintains a nonthrombotic, nonadhesive surface with appropriate vascular wall smooth muscle tone. Injury or exposure to certain mediators results in endothelial activation, a state where endothelial cells develop a procoagulant surface that can be adhesive for inflammatory cells, and also express factors that cause smooth muscle contraction and/or proliferation and matrix synthesis. VEGF, vascular endothelial growth factor.

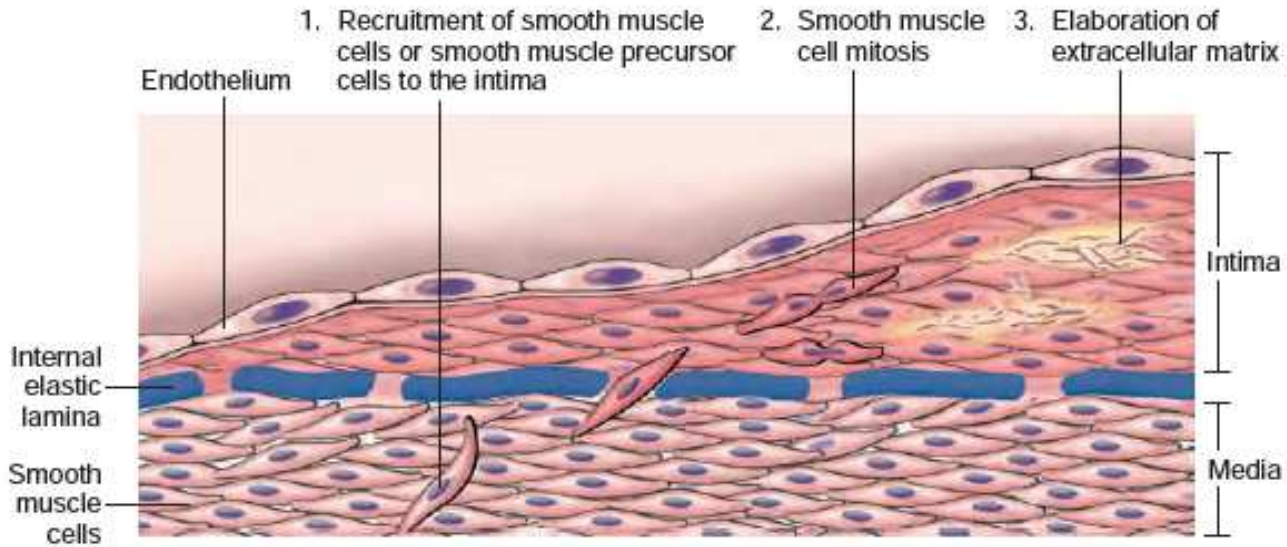
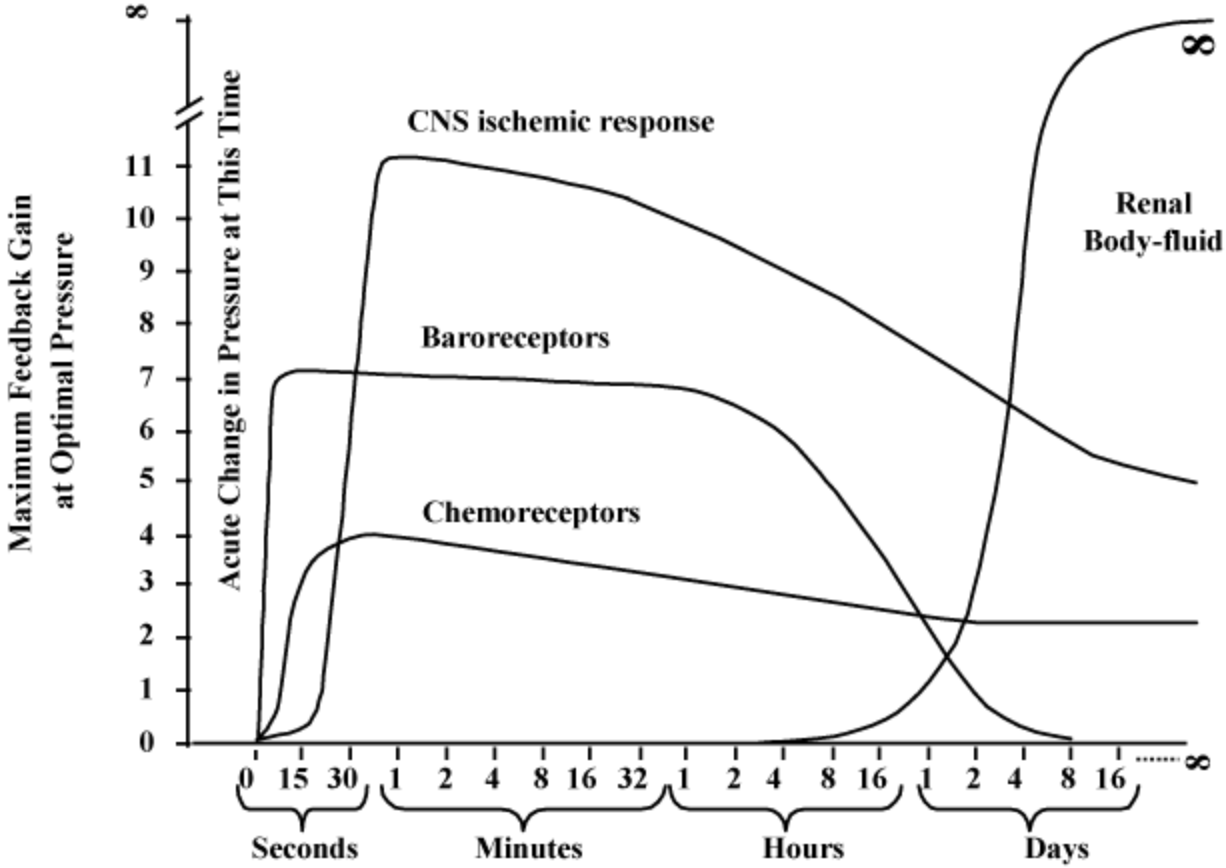


Figure 11-3 Stereotypical response to vascular injury. Schematic diagram of intimal thickening, emphasizing intimal smooth muscle cell migration and proliferation associated with extracellular matrix synthesis. The new intimal cells are shown in a different color to emphasize that they have a proliferative, synthetic, and noncontractile phenotype distinct from medial smooth muscle cells.

Table 11-1 Types and Causes of Hypertension (Systolic and Diastolic)

Essential hypertension
Accounts for 90% to 95% of all cases
Secondary hypertension
Renal
Acute glomerulonephritis Chronic renal disease Polycystic disease Renal artery stenosis Renal vasculitis Renin-producing tumors
Endocrine
Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia, licorice ingestion) Exogenous hormones (glucocorticoids, estrogen [including pregnancy-induced and oral contraceptives], sympathomimetics and tyramine-containing foods, monoamine oxidase inhibitors) Pheochromocytoma Acromegaly Hypothyroidism (myxedema) Hyperthyroidism (thyrotoxicosis) Pregnancy-induced
Cardiovascular
Coarctation of aorta Polyarteritis nodosa Increased intravascular volume Increased cardiac output Rigidity of the aorta
Neurologic
Psychogenic Increased intracranial pressure Sleep apnea Acute stress, including surgery

Blood pressure control mechanisms

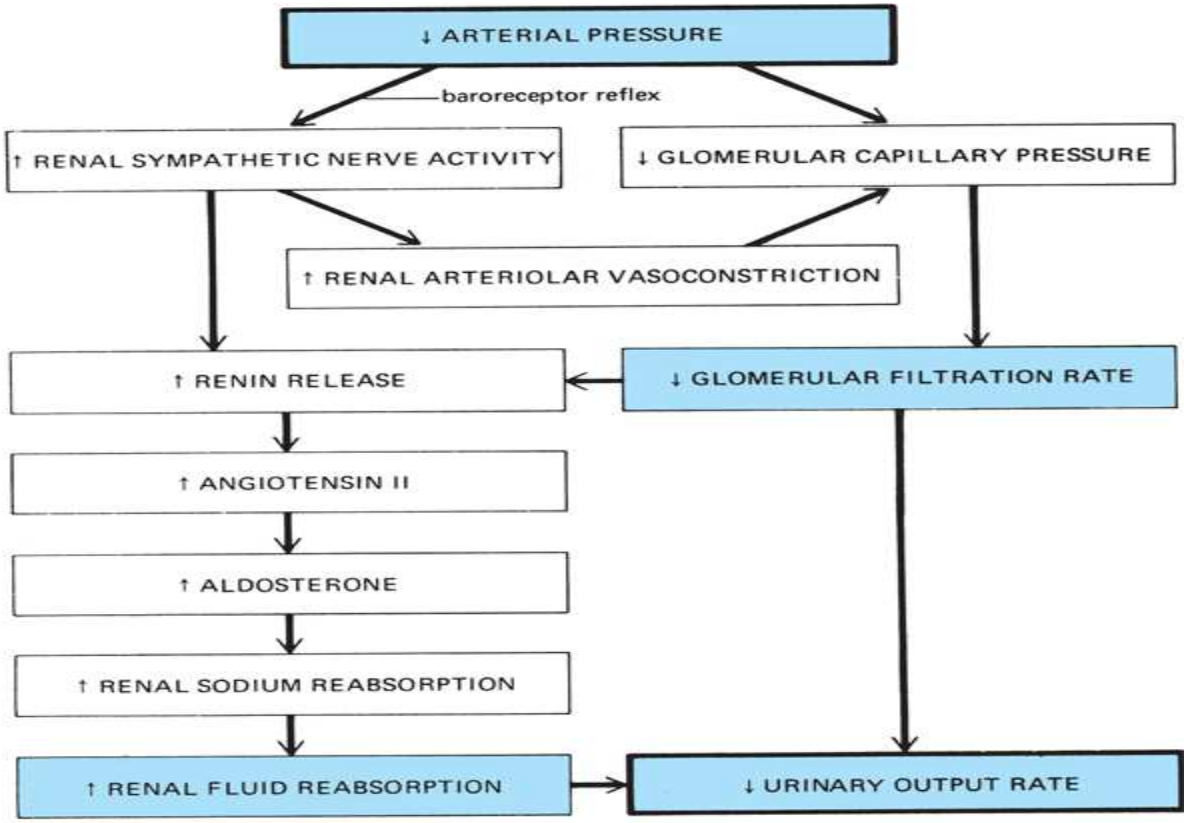


Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart,* 12th Edition: http://www.accessmedicine.com

Source: Redrawn from Guyton AC, Hall JE. *Textbook of Medical Physiology,* 11th ed. Philadelphia: Elsevier, 2006, p. 230.

Fig. 69-3 Accessed 04/01/2010

Homeostatic mechanism



Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th Edition: http://www.accessmedicine.com

Fig. 9-9 Accessed 02/01/2010

Marked changes in fluid intake rate have rather minor influences on the arterial pressure of a normal individual.

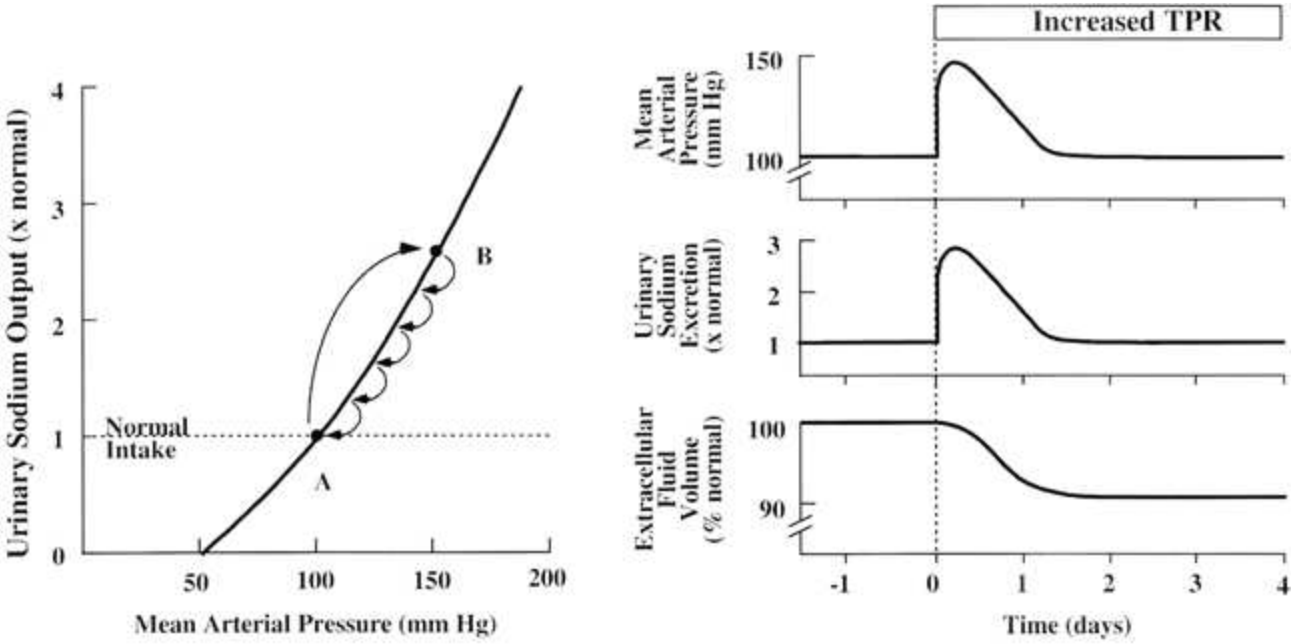
Arterial pressure and peripheral vascular resistance

- If the kidneys are functioning normally, with a change in total peripheral vascular resistance and concomitant reciprocal effect on cardiac output, there is no long-term effect on arterial pressure.
- The renal–body fluid feedback control mechanism does not stop functioning until the arterial pressure returns all the way back to its original control level.
- There is a shift of pressure natriuresis that appears to initiate and sustain the hypertension.

Pathogenesis of hypertension

- 70% of the causes of renovascular hypertension are due to arteriosclerosis of the renal artery (with renal artery stenosis).
- Fibromuscular hyperplasia of the artery is also described.
- Renin secretion increases.
- Increased arteriolar resistance (afterload) leads to cardiac hypertrophy.
- Increased circulating volume (preload) leads to dilated ventricle.

Long-term effects of increased peripheral vascular resistance



If there is no change in natriuresis, elevated blood pressure cannot be sustained because Na^+ excretion exceeds intake, reducing fluid volume until blood pressure returns to normal and sodium balance is re-established. Sodium sensitive only if functional nephron loss.

Source. Redrawn from Hall JE. The kidney, hypertension, and obesity. *Hypertension* 2003;41:625–633.
Fig. 69-5 Accessed 04/01/2010

Arterial pressure and urinary excretion of Na^+

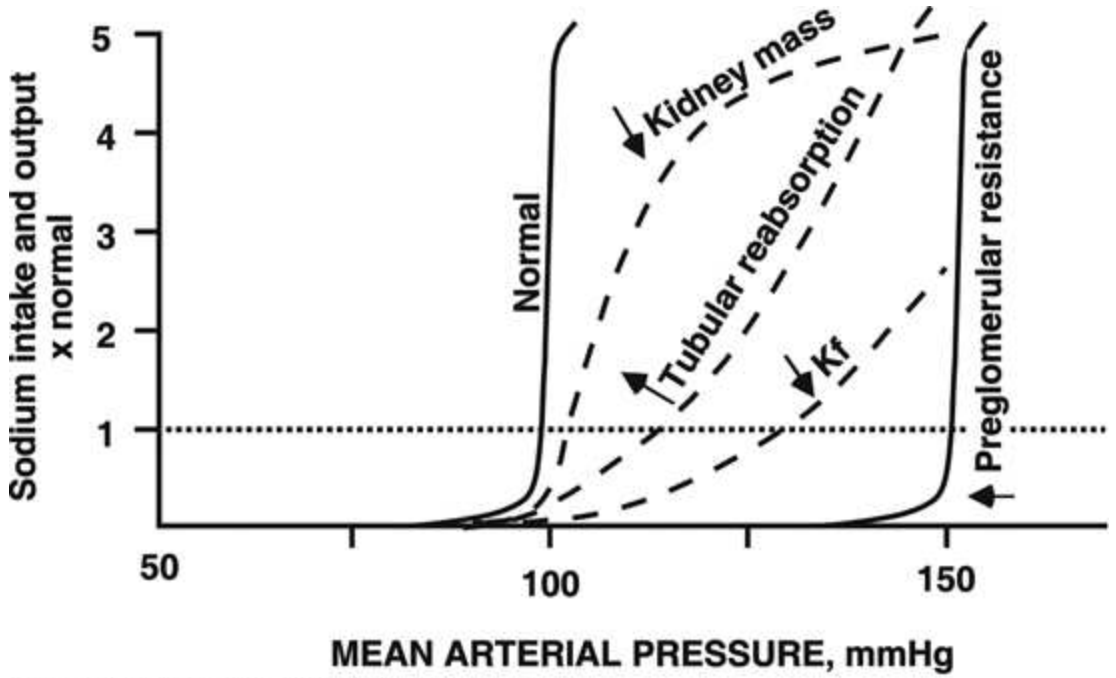


Fig. 69-6 Accessed 04/01/2010

Note that increased preglomerular resistance causes salt-insensitive hypertension, whereas the other renal abnormalities cause salt-sensitive hypertension.

Arterial pressure and Na^+ intake and excretion

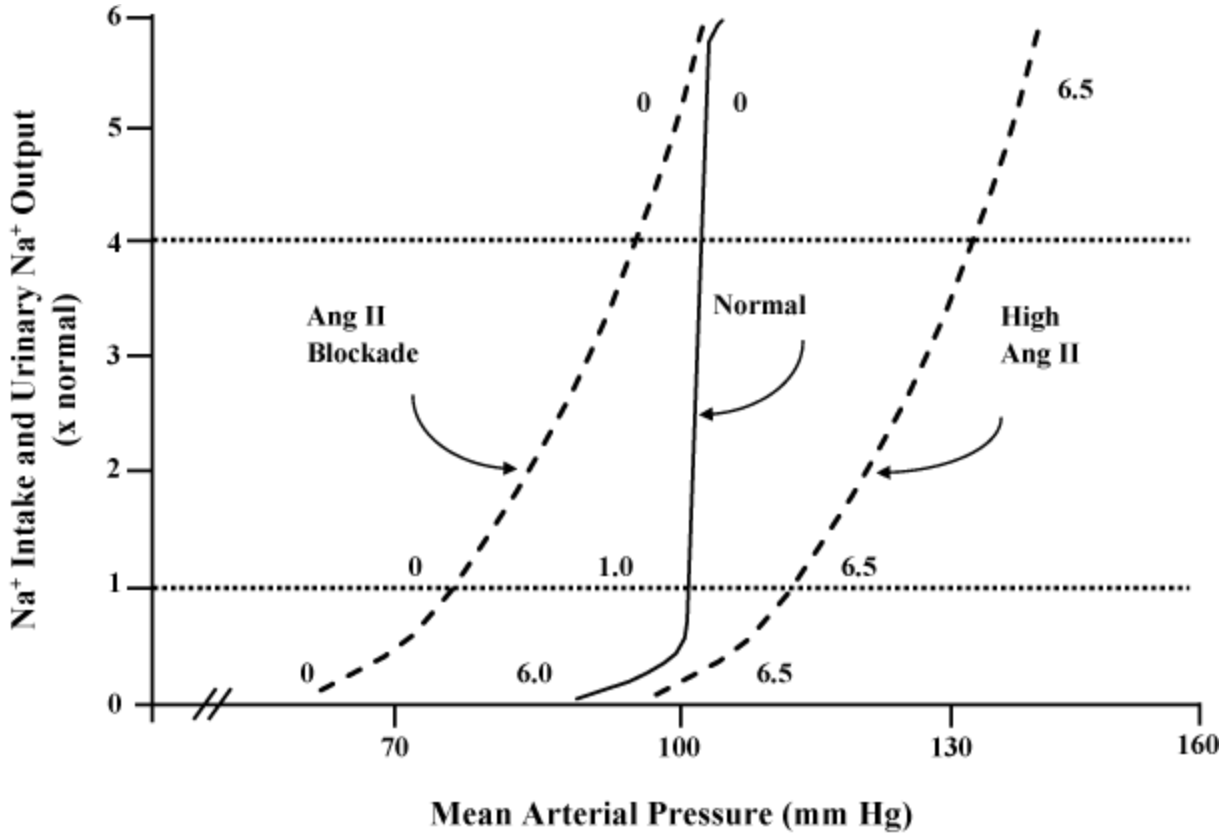
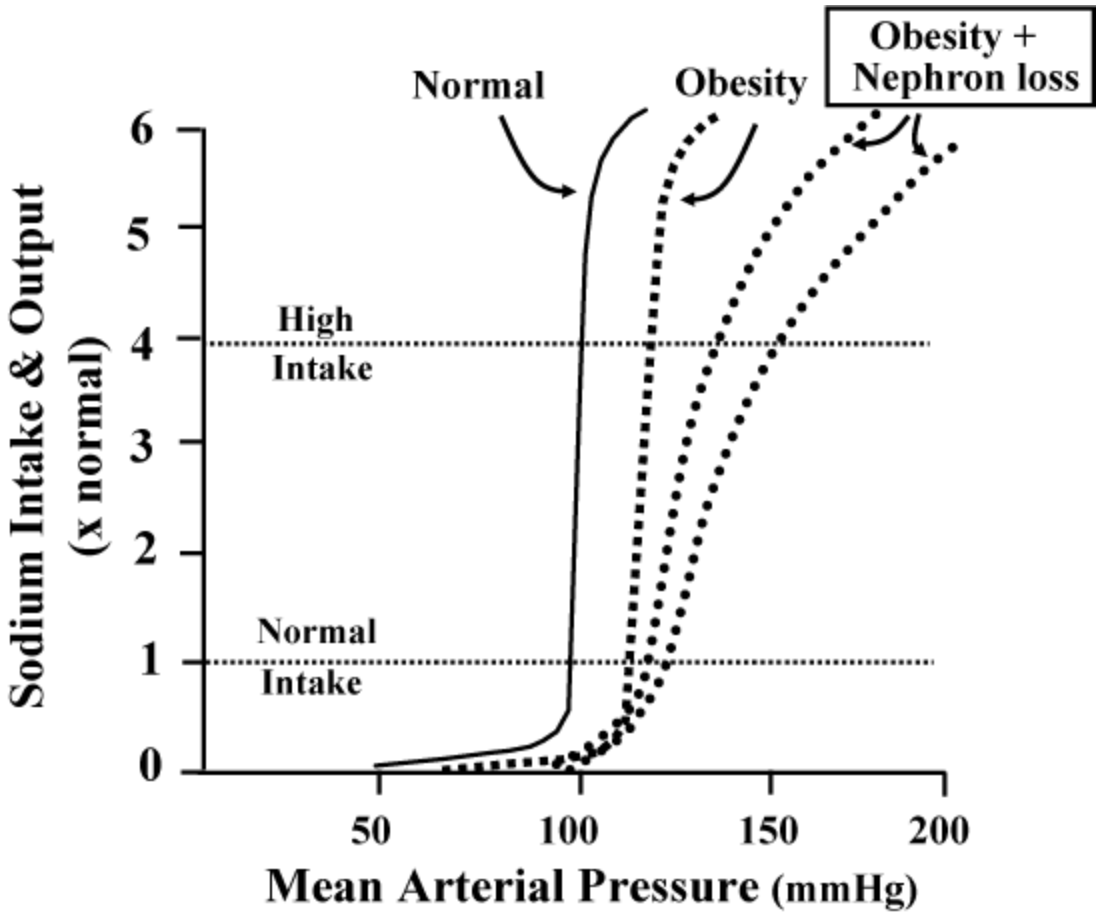


Fig. 69-9 Accessed 04/01/2010

Source: Redrawn from Hall JE, Guyton AC, Smith MJ Jr, et al. Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. *Am J Physiol* 1980;239:F271–F280.

Obesity, renal pressure, natriuresis



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson
P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

With chronic obesity lasting for many years, there may be a gradual loss of nephron function, further impairment of pressure natriuresis, increasing salt sensitivity, and higher arterial pressures.

Fig. 69-19
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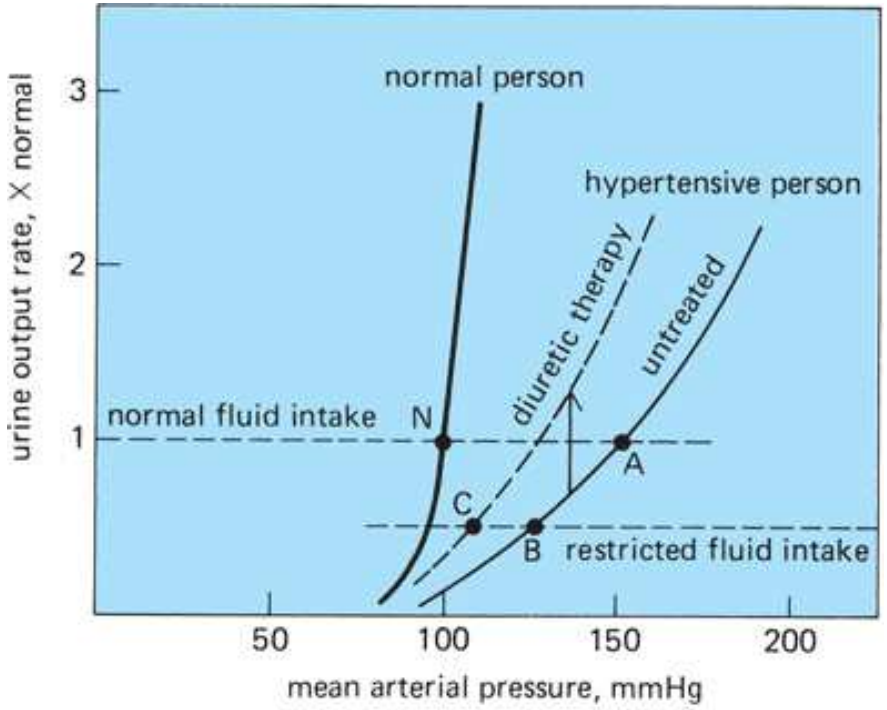
Renal function curves in hypertension and hypertension therapy



Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th Edition: http://www.accessmedicine.com

Fig. 11-5 Accessed 02/01/2010

Histopathology

- Hyaline arteriolosclerosis.
- Arterioles show homogeneous, pink hyaline thickening with associated luminal narrowing
- Changes reflect both plasma protein leakage across injured endothelial cells, as well as increased smooth muscle cell matrix synthesis in response to the chronic hemodynamic stresses of hypertension.

Histopathology

- Hyperplastic Arteriolosclerosis.
- This lesion occurs in severe hypertension
- Vessels exhibit concentric, laminated ("onion-skin") thickening of the walls with luminal narrowing
- The laminations consist of smooth muscle cells with thickened, reduplicated basement membrane
- In malignant hypertension, they are accompanied by fibrinoid deposits and vessel wall necrosis (necrotizing arteriolitis)

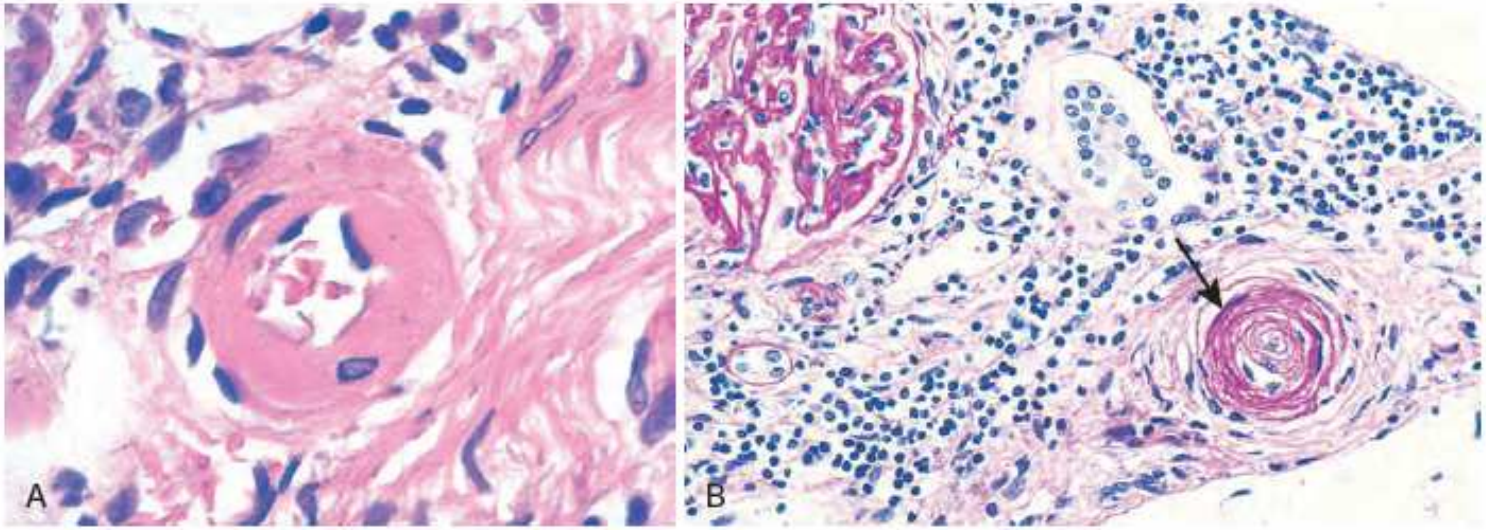
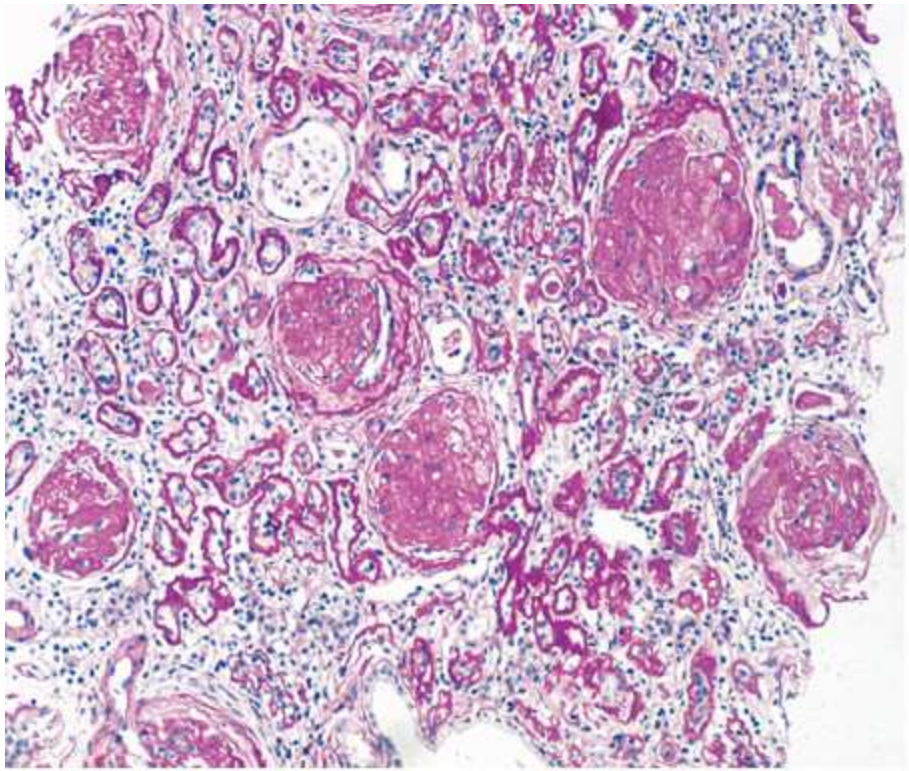


Figure 11-6 Vascular pathology in hypertension. **A,** Hyaline arteriolosclerosis. The arteriolar wall is thickened with increased protein deposition (hyalinized), and the lumen is markedly narrowed. **B,** Hyperplastic arteriolosclerosis (onion-skinning) causing luminal obliteration (periodic acid–Schiff [PAS] stain). (Courtesy Helmut Rennke, MD, Brigham and Women's Hospital, Boston, Mass.)

Arteriolar nephrosclerosis



Hypertension-associated injury often manifests extensive global sclerosis of glomeruli, with accompanying and proportional tubulointerstitial fibrosis and pericapsular fibrosis, and there may be segmental sclerosis.

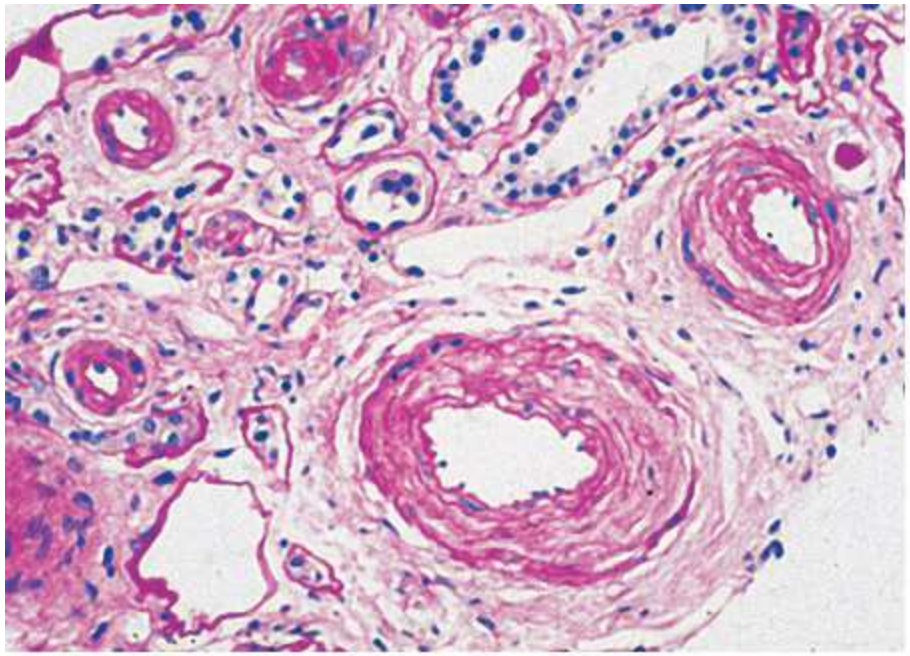
(ABF/Vanderbilt Collection.)

Fig. e9-19 Accessed 03/17/2010

Hypertensive emergency

- Defined as uncontrolled hypertension that will lead to acute organ damage if not controlled within one hour or presentation.
- Use agents with short half-life.
- Diuretics may compound the problem as increased movement of fluid through the kidney is sensed by the macula densa.
- Sympathetic activity is increased (as with low $Na^{\pm}$ state) and vasoconstriction results.
- Lower mean arterial pressure by 25% in the first two hours, achieving a blood pressure of 160/100 mmHg within 6 hours.

Malignant hypertension



The vessels show disproportionately severe changes of intimal fibrosis, medial hypertrophy, and arteriolar hyaline deposits. Fibrinoid necrosis.

(ABF/Vanderbilt Collection.)

Fig. e9-20 Accessed 03/17/2010

Arterial vascular disease

- Arteriolosclerosis affects small arteries and arterioles, and may cause downstream ischemic injury.
- Mönckeberg medial sclerosis is characterized by calcification of the walls of muscular arteries, typically involving the internal elastic membrane
- >50 years of age
- Does not obstruct lumen nor impair flow
- Limb arteries usual sites
- Circumferential

Arterial vascular disease

- An atheromatous plaque consists of a raised lesion with a soft grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a fibrous cap
- Inflammation is present at all stages of atherogenesis

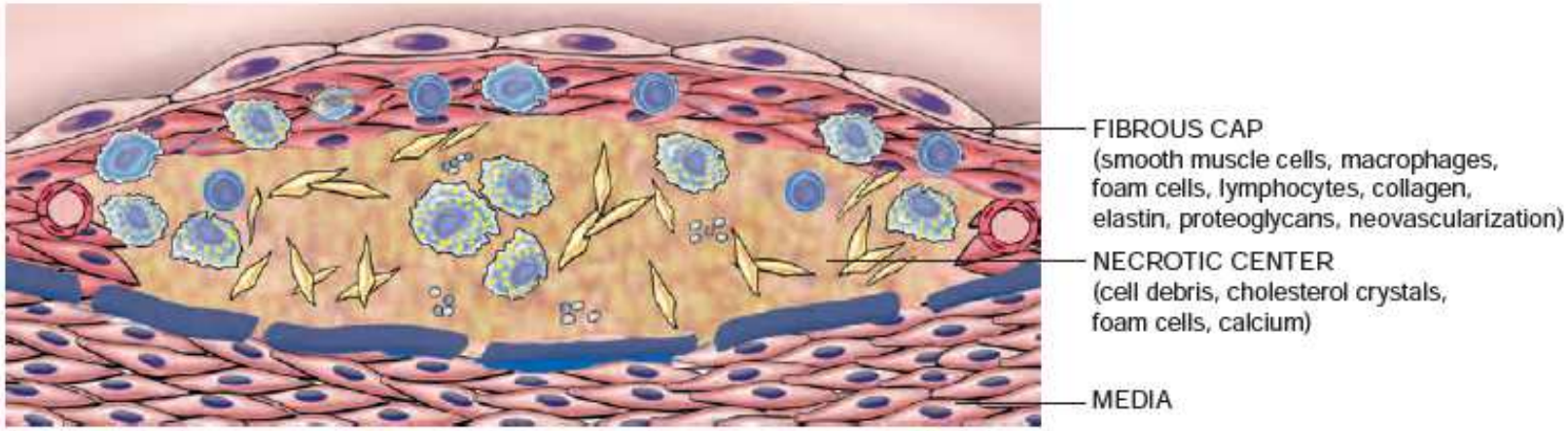


Figure 11-7 Basic structure of an atherosclerotic plaque. Note that atherosclerosis is an intimal-based process.

Atherosclerosis risk

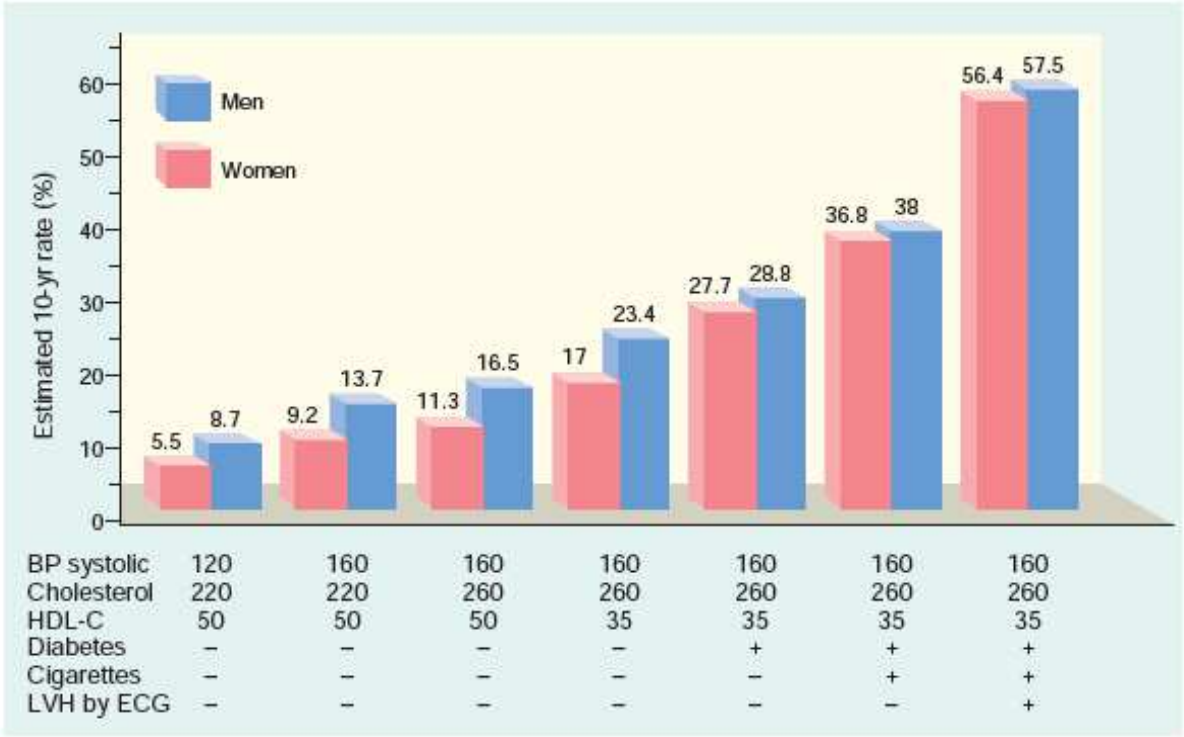


Figure 11-8 Estimated 10-year rate of coronary artery disease in 55-year old men and women as a function of established risk factors (hyperlipidemia, hypertension, smoking, and diabetes). BP, Blood pressure; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy. (From O'Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: Lessons from observational studies. J Hypertension 16 (Suppl. 6):3, 1998.)

Atherosclerosis risk

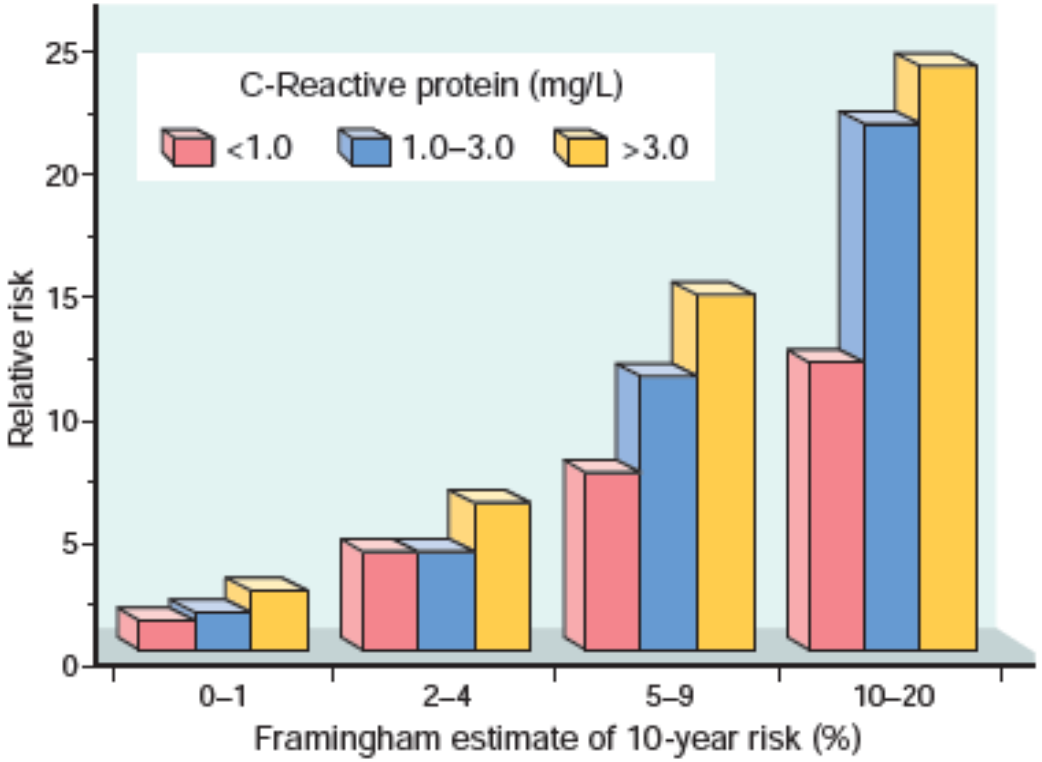


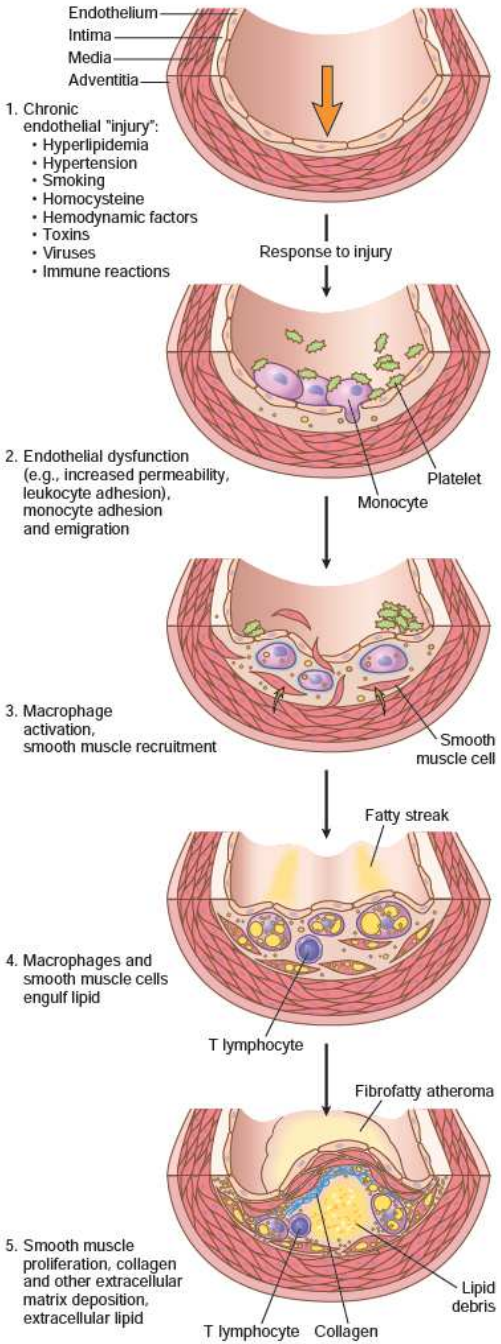
Figure 11-9 C reactive protein (CRP) predicts cardiovascular risk. Relative risk (y-axis) refers to the risk of a cardiovascular event (e.g., myocardial infarction). The x-axis is the 10-year risk of a cardiovascular event derived from established risk factors identified in the Framingham Heart Study. In each risk group, CRP values further stratify patients. (Data from Ridker PM, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347:1557, 2002.)

Atherosclerosis risk

- Serum homocysteine levels correlate with coronary atherosclerosis, peripheral vascular disease, stroke, and venous thrombosis
- Although low folate and vitamin B_{12} levels can increase homocysteine, supplemental vitamin ingestion does not affect the incidence of cardiovascular disease.
- Lipoprotein a (Lp(a)) is an altered form of LDL that contains the apoB-100 portion of LDL linked to apolipoprotein A (apo A)
- Resembles plasminogen
- Risk independent of total cholesterol or LDL levels.

Atherosclerosis risk

- Elevated PAF1 is a strong predictor of major cardiac events.
- PAF1 gene at 9q13.2 part of RNA polymerase complex
- Codes a ubiquitin ligase (apoptosis) as well as active in histone acetylation
- Needed to maintain embryonal cell pluripotency
- The amount of calcium in the coronary artery wall is a strong predictor of major cardiac events.


Endothelium
Intima
Media
Adventitia
1. Chronic endothelial "injury":
• Hyperlipidemia
• Hypertension
• Smoking
• Homocysteine
• Hemodynamic factors
• Toxins
• Viruses
• Immune reactions
Response to injury
Platelet
Monocyte
2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion), monocyte adhesion and emigration
3. Macrophage activation, smooth muscle recruitment
Smooth muscle cell
Fatty streak
4. Macrophages and smooth muscle cells engulf lipid
T lymphocyte
Fibrofatty atheroma
5. Smooth muscle proliferation, collagen and other extracellular matrix deposition, extracellular lipid
Lipid debris
T lymphocyte
Collagen

Vascular injury and repair

- Associated with endothelial cell dysfunction or loss
- Stimulates smooth muscle cell recruitment and proliferation and associated matrix synthesis
- Neo-intimal smooth muscle cells are motile, undergo cell division, and acquire new biosynthetic capabilities.
- Regulated by local growth factor and cytokine secretion of inflammatory cells
- Results in intimal thickening.
- Fibromuscular hyperplasia is a developmental defect.

Atherosclerosis

- Intimal injury.
- Endothelial cell dysfunction leads to expression of:
- Adhesion molecules
- Monocyte adhesion to endothelium
- Platelet adhesion and release of cytokines
- Clot formation
- Erythrocyte membranes are rich in cholesterol
- Accumulation of oxidized LDL particles in macrophages (foam cell formation).
- Smooth muscle cell migration is stimulated by PDGF and FGF-β.
- Chronic inflammatory state.
- Fibrous plaque forms.
- May be accelerated by carnitine.

Atherosclerosis

- Calcification may be seen in plaque.
- Fixed obstruction in coronary artery (>70% stenosis) will cause chest pain if Oxygen demand increased.
- Resistance is proportional to lumen radius (r^4)
- If unobstructed, 100% flow,
- at 50% obstruction, resistance to flow increased 16 times
- at 70% obstruction, resistance to flow increased 125 times

Atherosclerosis

- Fatty streaks (collections of lipid laden macrophages in the intima) are the earliest lesions of atherosclerosis.
- Probably evolve into plaques.
- Atheromatous plaques are white-yellow and encroach on the lumen of the artery
- Superimposed thrombus over ulcerated plaques is red-brown
- Lesions are rarely circumferential.
- Abdominal aorta, epicardial coronary arteries, popliteal arteries, internal carotid arteries, and the Circle of Willis are likely sites of involvement (in descending order).

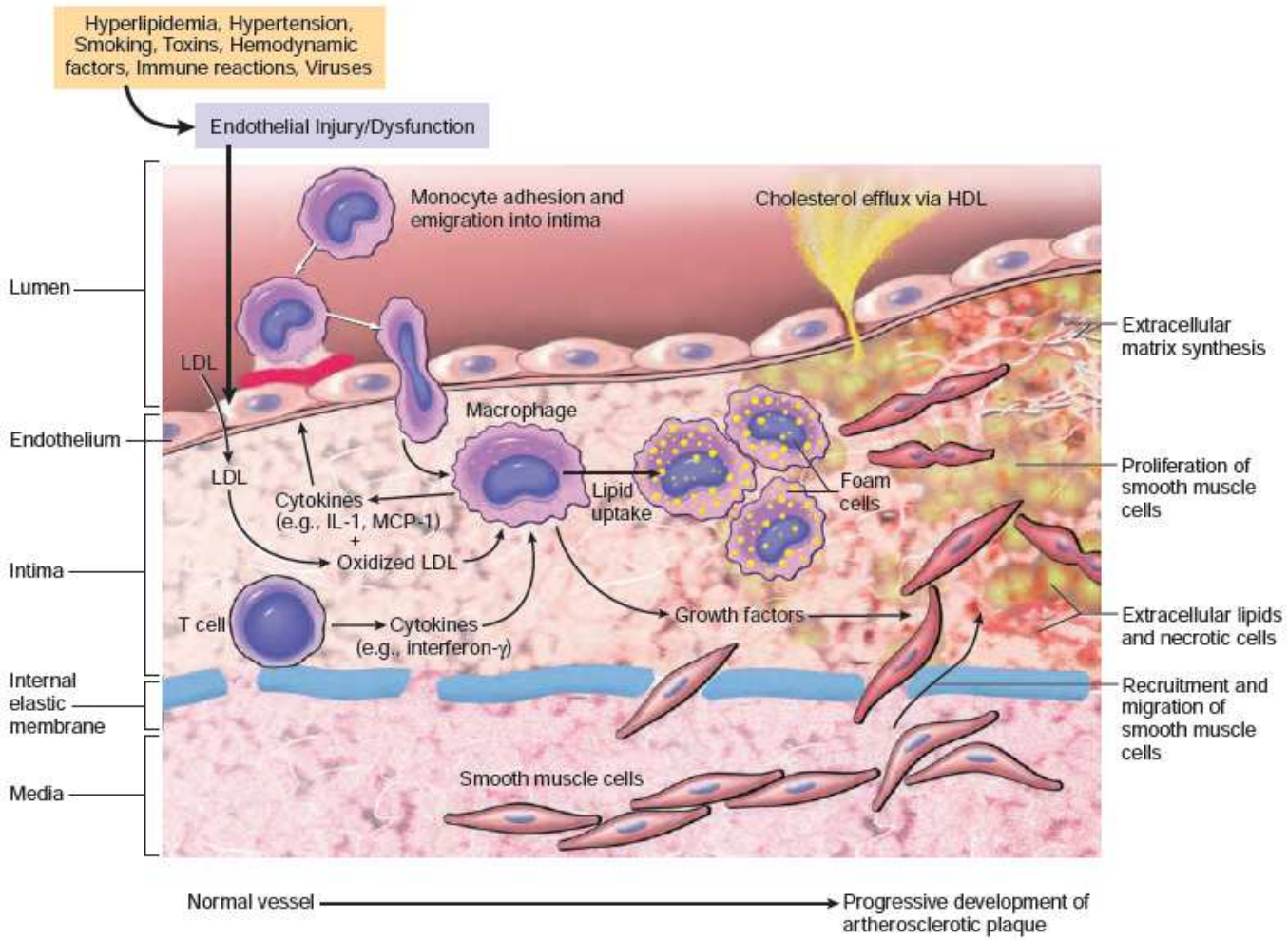


Figure 11-11 Sequence of cellular interactions in atherosclerosis. Hyperlipidemia, hyperglycemia, hypertension, and other influences cause endothelial dysfunction. This results in platelet adhesion and recruitment of circulating monocytes and T cells, with subsequent cytokine and growth factor release from inflammatory cells leading to smooth muscle cell migration and proliferation as well as further macrophage activation. Foam cells in atheromatous plaques derive from macrophages and smooth muscle cells that have accumulated modified lipids (e.g., oxidized and aggregated low density lipoprotein [LDL]) via scavenger and LDL-receptor-related proteins. Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia, as well as from degenerating foam cells. Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux; high-density lipoprotein (HDL) likely helps clear cholesterol from these accumulations. In response to the elaborated cytokines and chemokines, smooth muscle cells migrate to the intima, proliferate, and produce extracellular matrix, including collagen and proteoglycans. IL-1, interleukin-1; MCP-1, monocyte chemoattractant protein-1.

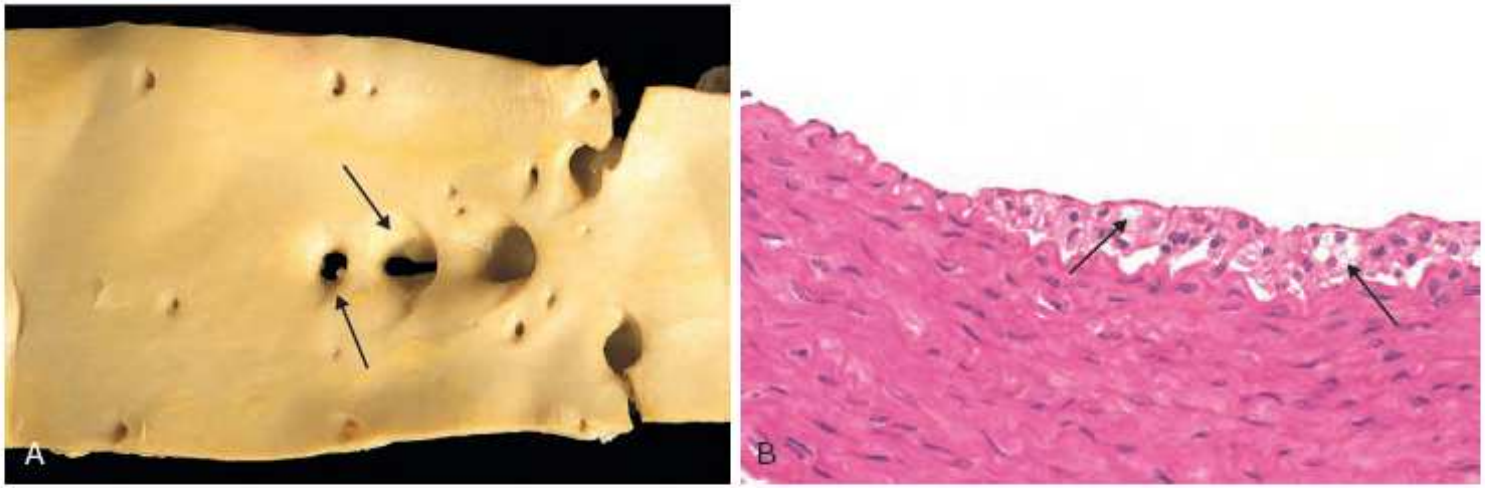


Figure 11-12 Fatty streak, a collection of foamy macrophages in the intima. **A,** Aorta with fatty streaks *(arrows),* associated largely with the ostia of branch vessels. **B,** Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal, macrophage-derived foam cells *(arrows).* (**B,** Courtesy Myron I. Cybulsky, MD, University of Toronto, Canada.)

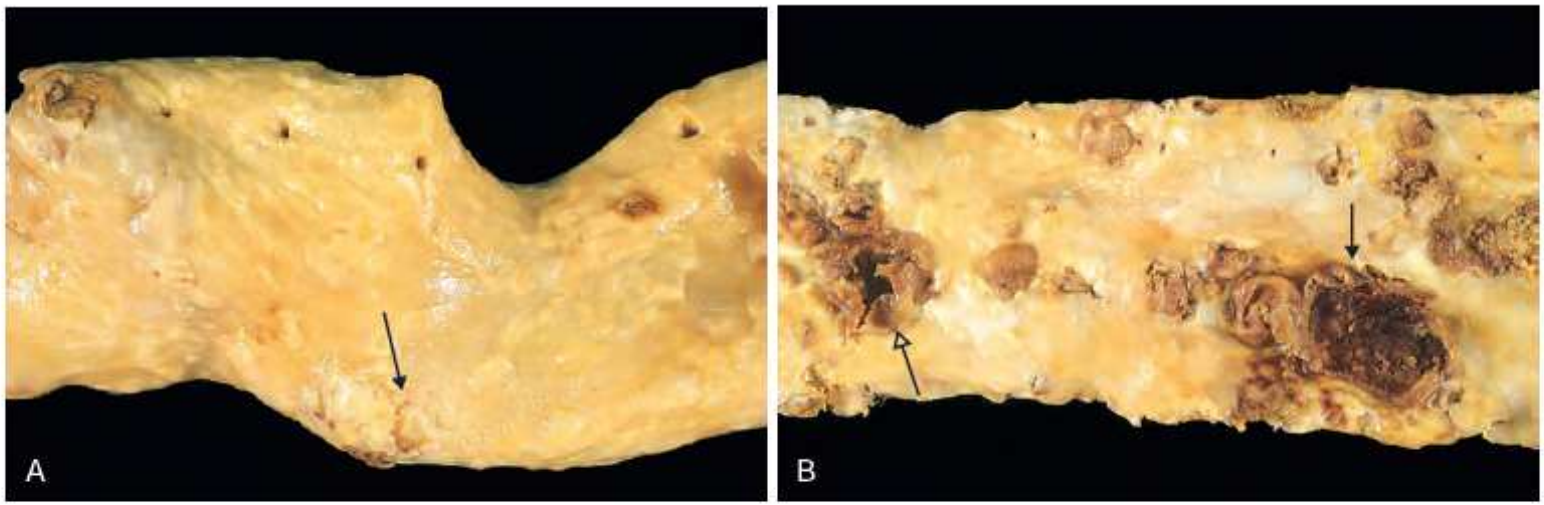


Figure 11-13 Gross views of atherosclerosis in the aorta. **A,** Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the arrow. **B,** Severe disease with diffuse and complicated lesions including an ulcerated plaque *(open arrow),* and a lesion with overlying thrombus *(closed arrow).*

Histopathology

- Atherosclerotic plaques have three principal components:
- (1) smooth muscle cells, macrophages, and T cells
- (2) extracellular matrix, including collagen, elastic fibers, and proteoglycans
- (3) intracellular and extracellular lipid

Histopathology

- There is a superficial fibrous cap composed of smooth muscle cells and relatively dense collagen.
- Beneath and to the side of the cap (the “shoulder”) is a more cellular area containing macrophages, T cells, and smooth muscle cells.
- Deep to the fibrous cap is a necrotic core, containing lipid (primarily cholesterol and cholesterol esters), debris from dead cells, foam cells (lipid laden macrophages and smooth muscle cells), fibrin, and other plasma proteins.
- Thrombus may be present.
- The periphery of the lesions demonstrate neovascularization (proliferating small blood vessels)

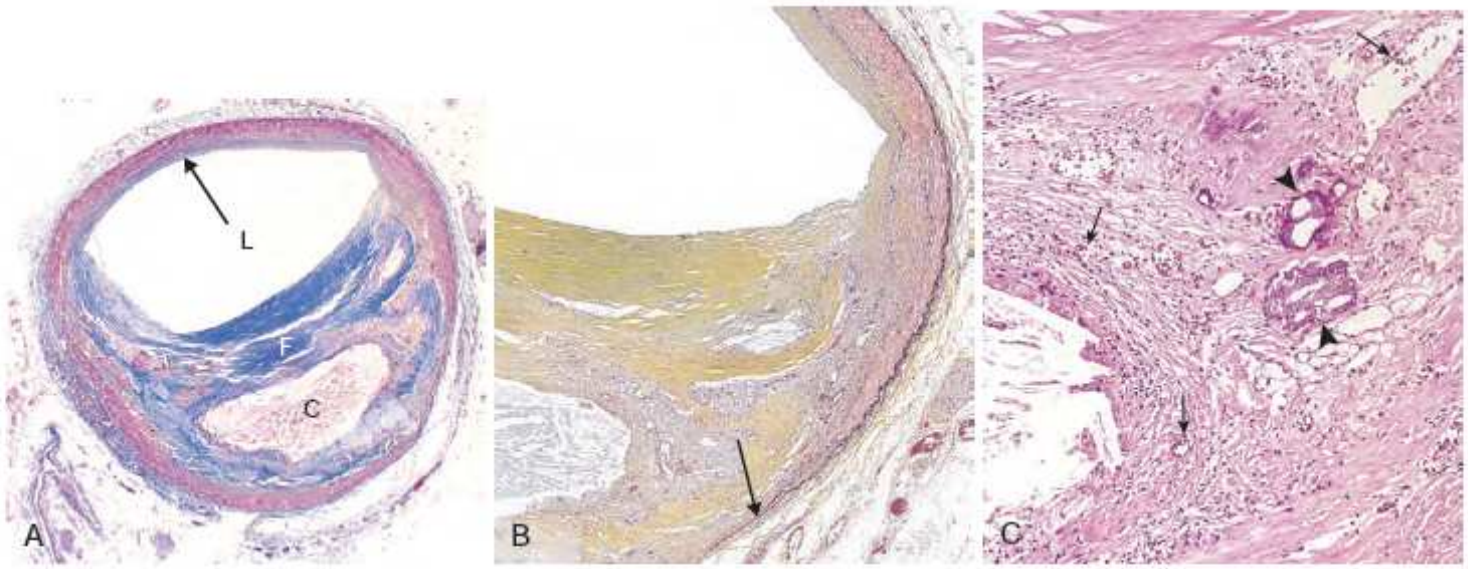


Figure 11-14 Histologic features of atheromatous plaque in the coronary artery. **A,** Overall architecture demonstrating fibrous cap (F) and a central necrotic core (C) containing cholesterol and other lipids. The lumen (L) has been moderately compromised. Note that a segment of the wall is plaque free *(arrow)*; the lesion is therefore "eccentric." In this section, collagen has been stained blue (Masson trichrome stain). **B,** Higher-power photograph of a section of the plaque shown in **A,** stained for elastin (black), demonstrating that the internal and external elastic laminae are attenuated and the media of the artery is thinned under the most advanced plaque *(arrow)*. **C,** Higher magnification photomicrograph at the junction of the fibrous cap and core, showing scattered inflammatory cells, calcification *(arrowhead)*, and neovascularization *(small arrows)*.

Plaque complications

- Rupture, ulceration, or erosion of the surface of atheromatous plaques exposes highly thrombogenic substances
- Leads to thrombosis (and vessel occlusion)
- Hemorrhage into a plaque because of rupture of overlying fibrous cap or thin walled new vessels may also lead to vessel occlusion
- Plaque rupture may lead to atheromatous emboli.
- Atherosclerosis-induced pressure or ischemic atrophy of the underlying media, with loss of elastic tissue, causes weakness (aneurysm) and potential rupture.

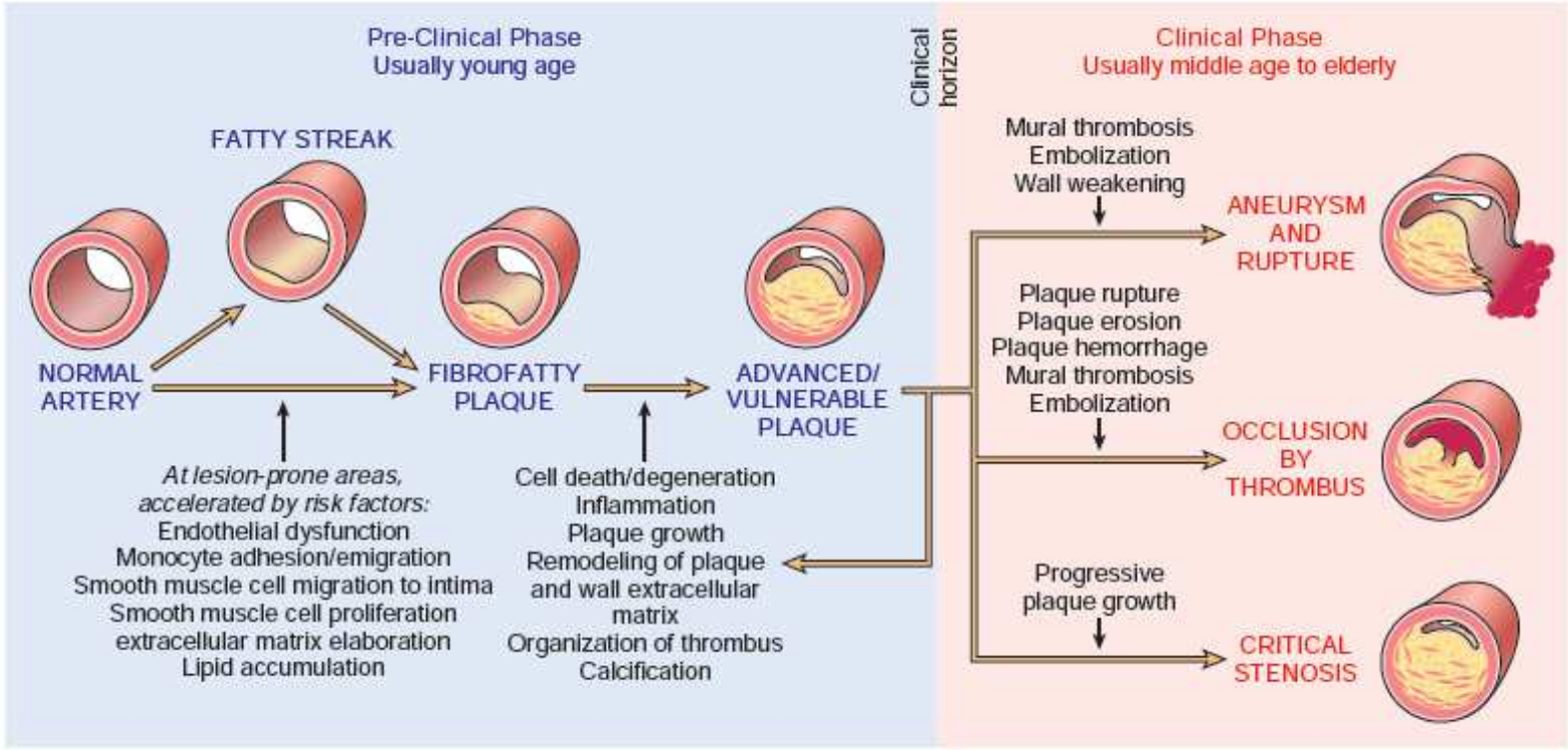


Figure 11-16 The natural history, morphologic features, main pathogenic events, and clinical complications of atherosclerosis.

Plaque complications

- Plaques that are responsible for myocardial infarction and other acute coronary syndromes are often asymptomatic before the acute change
- The fibrous cap undergoes continuous remodeling that can stabilize the plaque, or conversely, render it more susceptible to rupture.
- Plaques rupture when they are unable to withstand mechanical stresses generated by vascular shear forces.
- Adrenergic stimulation can increase systemic blood pressure or induce local vasoconstriction, thereby increasing the physical stresses on a given plaque

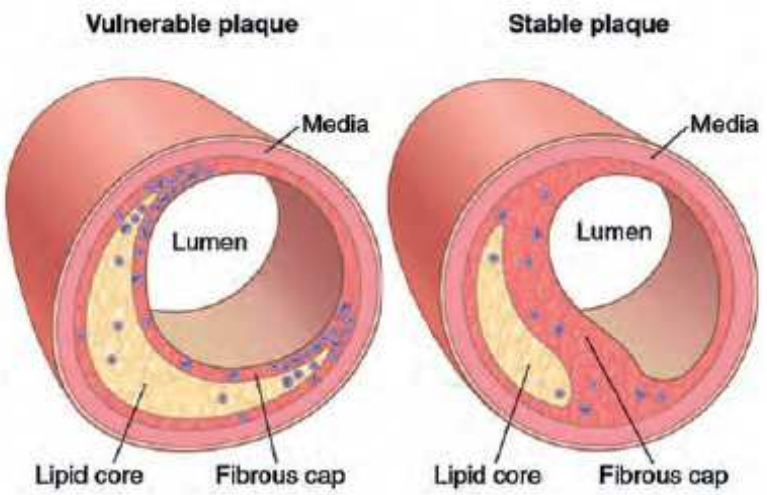
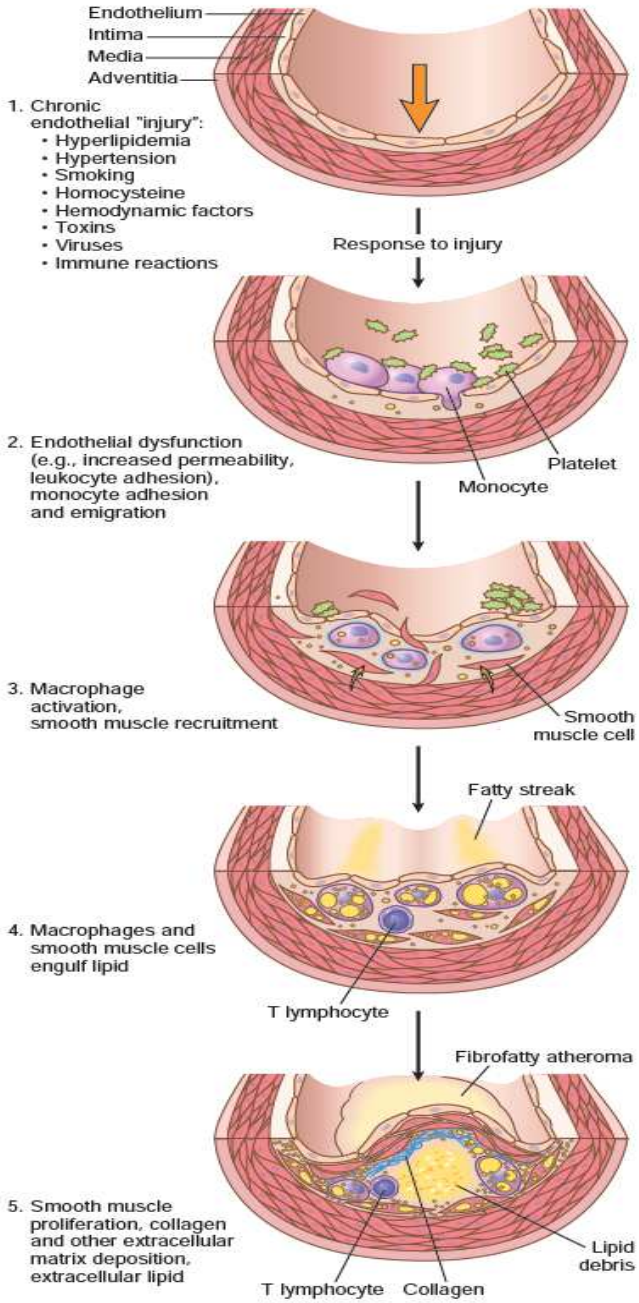


Figure 11-17 Vulnerable and stable atherosclerotic plaque. *Vulnerable plaques* have thin fibrous caps, large lipid cores, and greater inflammation. Stable plaques have thickened and densely collagenous fibrous caps with minimal inflammation and underlying atheromatous core. (Adapted from Libby P: Circulation 91:2844, 1995.)


Endothelium
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1. Chronic endothelial "injury":
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• Smoking
• Homocysteine
• Hemodynamic factors
• Toxins
• Viruses
• Immune reactions
Response to injury
2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion), monocyte adhesion and emigration
Platelet
Monocyte
3. Macrophage activation, smooth muscle recruitment
Smooth muscle cell
Fatty streak
4. Macrophages and smooth muscle cells engulf lipid
T lymphocyte
Fibrofatty atheroma
5. Smooth muscle proliferation, collagen and other extracellular matrix deposition, extracellular lipid
Lipid debris
T lymphocyte
Collagen

Cholesterol levels

- Desirable cholesterol levels (consensus):
- Up to 200 mg/dl for total cholesterol
- Up to 100 mg/dl for LDL cholesterol
- Not less than 50 mg/dl for HDL cholesterol
- When plasma cholesterol concentrations exceed these levels, it is referred to as hypercholesterolemia.
- Diet, exercise, and other non-pharmacological methods are first choices for therapy
- Statins are indicated in cases of primary hypercholesterolemia and mixed dyslipidemia in patients who do not respond to those measures.

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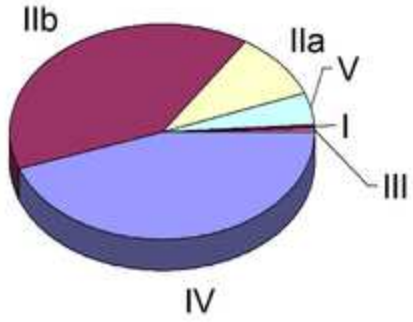
Familial dyslipidemias



Hyperlipo-proteinemia		OMIM	Synonyms	Defect	Increased lipoprotein	Main symptoms	Treatment	Serum appearance	Estimated prevalence
Type I	a	238600	Buerger-Gruetz syndrome or familial hyperchylomicronemia	Decreased lipoprotein lipase (LPL)	Chylomicrons	Acute pancreatitis, lipemia retinalis, eruptive skin xanthomas, hepatosplenomegaly	Diet control	Creamy top layer	One in 1,000,000[9]
	b	207750	Familial apoprotein CII deficiency	Altered ApoC2					
	c	118830		LPL inhibitor in blood					
Type II	a	143890	Familial hypercholesterolemia	LDL receptor deficiency	LDL	Xanthelasma, arcus senilis, tendon xanthomas	Bile acid sequestrants, statins, niacin	Clear	One in 500 for heterozygotes
	b	144250	Familial combined hyperlipidemia	Decreased LDL receptor and increased ApoB	LDL and VLDL		Statins, niacin, fibrate	Turbid	One in 100
Type III		107741	Familial dysbetalipoproteinemia	Defect in Apo E 2 synthesis	IDL	Tuboeruptive xanthomas and palmar xanthomas	Fibrate, statins	Turbid	One in 10,000[10]
Type IV		144600	Familial hypertriglyceridemia	Increased VLDL production and decreased elimination	VLDL	Can cause pancreatitis at high triglyceride levels	Fibrate, niacin, statins	Turbid	One in 100
Type V		144650		Increased VLDL production and decreased LPL	VLDL and chylomicrons		Niacin, fibrate	Creamy top layer and turbid bottom	

Familial hypertriglyceridemia Type I

- Ia LPL deficiency (lipoprotein lipase)
- Unable to process triglycerides for energy use
- Ib APOC2 mutation affects triglyceride transport as well as activates LPL
- Ic LPL inhibitor
- Triglycerides increased (chylomicra)
- Heterozygotes: 250-500mg/dL
- Homozygotes: 500-1000mg/dL
- Risk for pancreatitis at levels > 1000mg/dL
- May see steatosis, retinal vein occlusion, xanthomas
- Standing serum shows creamy top layer

Familial hypercholesterolemia Type IIa

- Accelerated atherosclerosis.
- Xanthomata in skin, tendons and under the eyes. Arcus senilis.
- Autosomal dominant.
- 5% of those under age 60 suffering myocardial infarction (early onset disease)
- Higher prevalence in French Canadians, South Africans and those on Mount Lebanon.

Familial hypercholesterolemia Type IIa

- Homozogytes may present with serum cholesterol >600 mg/dL.
- LDL increased.
- Death by age 30 if no intervention.
- Heterozygotes may present with serum cholesterol 300-400 mg/dL.
- Defect in LDL receptor gene.
- Clear serum

Familial combined hyperlipidemia Type IIb

- 15% of infarction before age 60
- 1 in 100 patients
- Increased LDL, VLDL, acetyl CoA
- Autosomal dominant
- Turbid serum
- Elevated APOB levels pathognomonic
- LPL and LDLR mutations most common
- USF 1 gene master regulator of lipid and carbohydrate metabolism (APOA5 one of genes controlled)

Familial combined hyperlipidemia Type IIb

- FADS 1-3 involved in the production of biologically active polyunsaturated fatty acids from plant sources as well as lipid homeostasis
- 40% of Chinese, Japanese, and Native Americans
- Point mutation that blocks conversion of plant sterols into longer length biologically active products such as EPA, DHA, and arachidonic acid
- Rare in Africans and Europeans

Familial dysbetalipoproteinemia Type III

- Xanthomata, orange creases in palmar skin
- Autosomal recessive
- Triglycerides and cholesterol elevated.
- ApoE E2/E2 deficiency.
- Interfaces with LDLR to facilitate transport into the cell.

Familial hypertriglyceridemia Type IV

- 1 in 100 patients
- Autosomal dominant.
- VLDL overproduction.
- Decreased clearance.
- Triglycerides elevated.

Type V

- VLDL overproduction.
- HDL diminished.
- Triglycerides elevated (chylomicra)
- Standing serum has creamy top layer, turbid bottom
- LPL diminished

Diet and heart disease

- DASH diet
- Eating vegetables, fruits, and whole grains
- Including fat-free or low-fat dairy products, fish, poultry, beans, and nuts
- Limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils such as coconut, palm kernel, and palm oils
- But vegetable oils (e.g., corn) replacing saturated fats are also associated with higher incidence of cardiovascular events
- Limiting sugar-sweetened beverages and sweets.

Diet and heart disease

- A vegan diet is more effective than the DASH diet
- Reducing daily sodium lowers blood pressure
- Major benefit to hypertensives
- 1500 mg sodium daily optimal
- Substituting protein for 10% of carbohydrates in diet is additionally effective in lowering blood pressure
- Glycemic index not related to blood pressure, lipid profile, or insulin resistance

Diet and heart disease

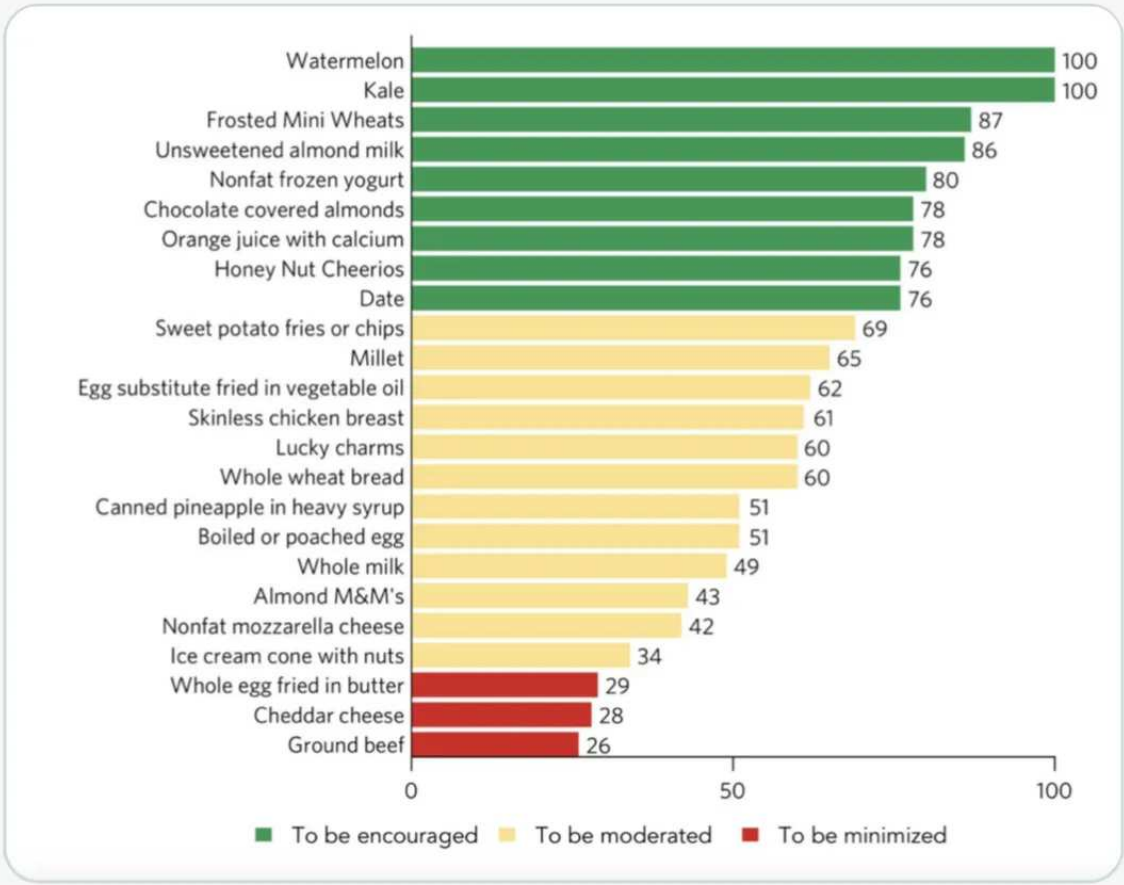
- No beneficial effects of reducing saturated fatty acid (SFA) intake on cardiovascular disease (CVD) and total mortality
- SFA protective effects against stroke.
- Although SFAs increase LDL cholesterol, due to increasing the number of large LDL particles, that LDL fraction is much less strongly related to CVD risk.
- It is also apparent that the health effects of foods cannot be predicted by their content in any nutrient group without considering the overall macronutrient distribution.

Diet and heart disease

- Whole-fat dairy, unprocessed meat, and dark chocolate are SFA-rich foods with a complex matrix that are not associated with increased risk of CVD.
- The amount of cholesterol consumed in the diet is not correlated with levels of blood cholesterol.
- The totality of available evidence does not support further limiting the intake of such foods
- J Am Coll Cardiol 2020 Aug 18;76(7):844-857. doi: 10.1016/j.jacc.2020.05.077

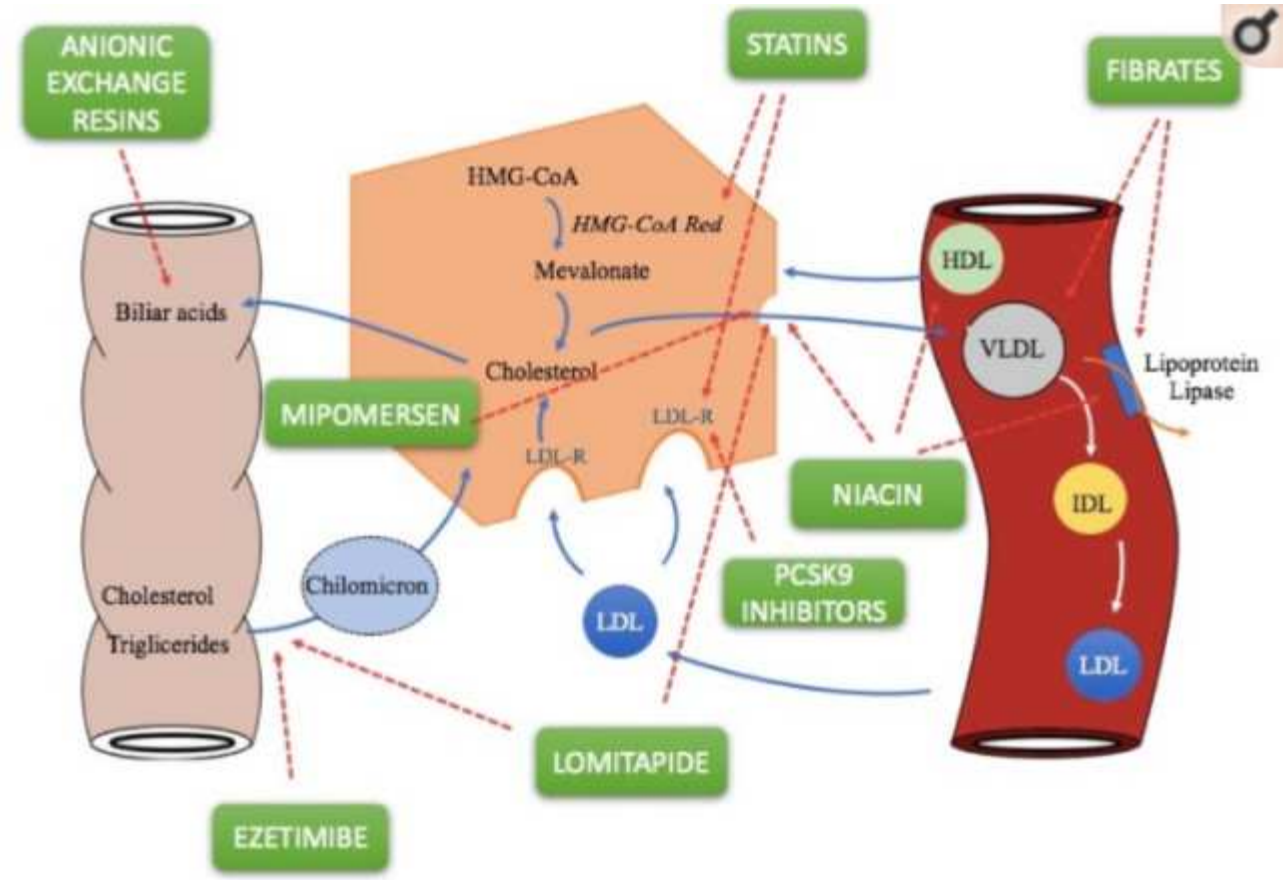
Nina Teicholz @bigfatsurprise · Jul 17

I'd like to feel optimistic about White House Conference on Nutrition in Sept., but guy in charge created this food ranking system:
Frosted Mini Wheats, Lucky charms >> whole egg
Ice cream w/ nuts > ground beef
Honey Nut Cheerios > egg fried in butter
osf.io/preprints/soca... 😆😭



Promote

458 925 2,328



doi: 10.3390/pharmacy6010010

Statins

- Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
- Selective and competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase
- The enzyme limits the conversion speed of HMG-CoA to mevalonic acid
- Mevalonic acid is a sterol precursor
- Inhibition of this enzyme initially leads to a reduction in liver cholesterol

Statins

- Compensatory mechanisms induce greater expression of both HMG-CoA reductase and LDL receptors
- By increasing receptor-mediated absorption of LDL, reduce plasma LDL.
- Also reduce VLDL and IDL precursors
- Further contributes to lowering plasma LDL-C
- Diminished production of mevalonic acid leads to diminished production (downstream) of farnesyl
- Leads to diminished dolichol production (and subsequent production of neuropeptides)
- May lead to increased tau protein production

Statins

- Anti-inflammatory effects
- Inhibits NF-kB (increase cancer risk)
- Lowers CRP
- CoQ_{10} deficiency results with statin use
- CYP34A metabolism
- Current calculators of CDV risk grossly overestimate risk

Statins

- Rhabdomyolosis is a potentially life-threating complication of statin use
- Muscle pain must not be ignored
- Do not use in pregnancy
- Associated with increased glucose and HbA_{1c} levels in diabetics
- Recommended “to stabilize plaque” as there is radiologic evidence of plaque shrinkage in patients with dyslipedemia.
- There are no “guidelines” for use in patients over 75 years of age.
- Benefit is minimal in all age groups (absolute risk reduction is approximately 1%)

Fibrates

- Fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil
- Exert their effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha)
- Bezafibrate is an agonist for all three PPAR isoforms (alpha, gamma and delta).
- Increase lipoprotein lipase (LPL) activity
- 100% oral bioavailability

Fibrates

- Decrease triglyceride levels and increase HDL levels
- The latter effect is more pronounced in patients with hypertriglyceridemia
- Reduce new-onset diabetes in those with metabolic syndrome

Bile acid-binding resins

- Cholestyramine, colesevelam, and colestipol
- Orally administered anion-exchange resins
- Are neither absorbed systemically nor metabolized by digestive enzymes.
- Bind to glycocholic acid and taurocholic acid in the intestine, making an insoluble complex that is excreted with the feces
- This leads to a continuous, though partial, removal of bile acids from the enterohepatic circulation.

Bile acid-binding resins

- The lower concentration of bile acids in the liver obstructs 7α-hydroxylase feedback inhibition, increasing the hepatic conversion of cholesterol to bile acids.
- LDL-C increases while total cholesterol falls
- Interfere with lipid soluble vitamin absorption

Sterol absorption inhibitors

- Ezetimibe
- Selectively inhibits the intestinal absorption of phytosterols and dietary cholesterol.
- Oral administration
- Locates on the small intestine brush lining and inhibits cholesterol absorption
- Decreases in intestinal cholesterol passage to the liver

Sterol absorption inhibitors

- Molecular target is NPC1L1 sterol transport , protein responsible for intestinal cholesterol capture and absorption of phytosterols.
- LDL uptake increases.
- Use with statin

Niacin

- Vitamin B3 (nicotinic acid)
- Significantly raises HDL levels while decreasing those of VLDL and LDL
- Prevents lipolysis in adipose tissue as it is a powerful inhibitor of the intracellular lipase system
- Vasodilation as side effect (minimize by taking 30 minutes before exposure to heat or sun)

Ω-3 fatty acids

- ω-3 (omega-3) fatty acids increase LDL diameter
- Reduce LDL atherogenicity without reducing its plasma levels
- Increase oxidation of fatty acids
- Modulating composition of membrane phospholipids

Testosterone

- Levels <5.3 nmol/L (153mg/dL) associated with increased risk of cardiovascular death
- Low levels of DHT (<0.59 nmol/L) and high levels of DHT (>2.45 nmol/L) associated with increased risk of cardiovascular death as well as all-cause mortality

Monoclonal antibodies

- IgG1 monoclonal antibody
- Binds with high affinity and specificity to PCSK9, inhibiting it.
- PCSK9 binds to LDL receptors on the surface of hepatocytes
- Promotes degradation of the receptors within the liver
- Reduce apo B as well as triglycerides
- 90% bioavailable orally

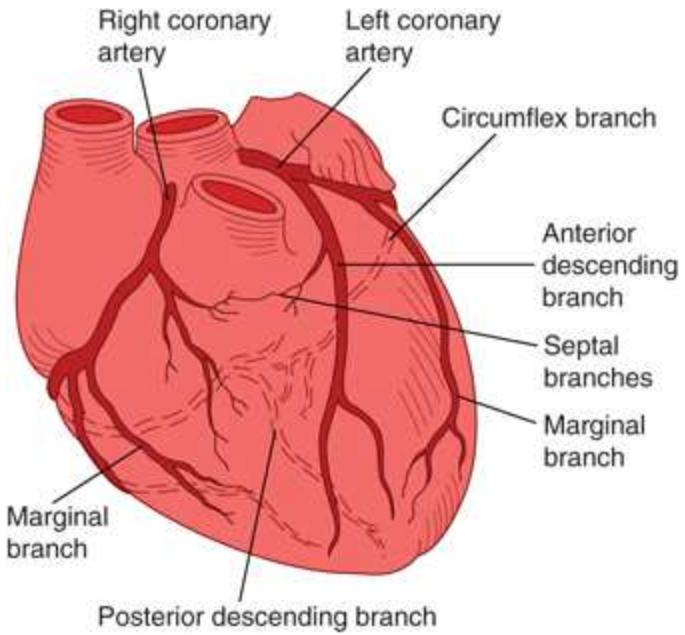
Microsomal transport protein inhibitor

- Lomitapide
- MTP is an intracellular protein found in the endoplasmic reticulum of liver and intestine cells which plays a role in the assembly of fats and their subsequent release into the blood.
- The inhibition of MTP reduces the production of chylomicrons in enterocytes and increases production of VLDL in hepatocytes independently of the LDL receptor
- 7% oral bioavailability
- CYP34A metabolism

apoB production inhibitor

- Mipomersen
- An antisense oligonucleotide that inhibits the production of apoB-100 by binding to the mRNA that encodes the synthesis of apoB
- apoB is an essential component of VLDL and LDL
- Up to 78% bioavailability when administered subcutaneously
- Protein bound

Coronary artery distribution



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Ross G: The cardiovascular system. In: *Essentials of Human Physiology.* Ross G [editor]. Copyright © 1978 by Year Book Medical Publishers.)

Fig. 34-11 Accessed 04/01/2010

Left coronary artery

- The Left Main Coronary Artery divides into the left circumflex and the left anterior descending coronary arteries
- Left Circumflex Coronary Artery.
- Follows atrio-ventricular groove.
- Supplies all the posterior left ventricular wall (not the apex) and part of the right ventricular wall.
- Obtuse marginal branch.

Left coronary artery

- Left Anterior Descending Coronary Artery.
- Follows the septum.
- Supplies the anterior left ventricular wall near the apex, the anterior portion (two-thirds) of the ventricular septum (right bundle branch), and the zpex (circumferentially).
- Septal perforating branches supply the AV node and the Bundle of His in 10% of hearts.

Right coronary artery

- The right coronary artery runs in the groove between the right atrium and ventricle.
- Proximally it gives off the right ventricular branches.
- Sinus nodal and atrio-ventricular nodal arterial branches
- Sinus nodal artery supplies the right atrial myocardium and the SA node.
- Atrio-ventricular nodal artery supplies the AV node and the Bundle of His (90% of hearts)

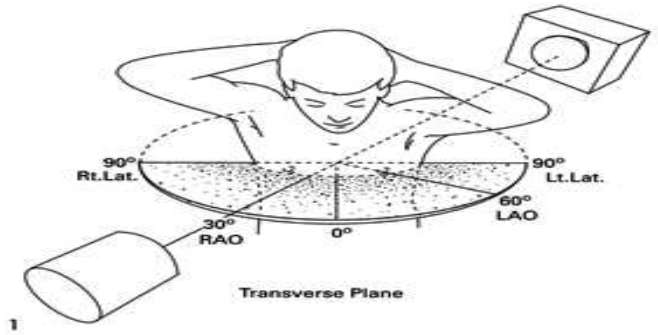
Right coronary artery

- Distally it divides at the posterior crossing point (crux) of the inter-ventricular and atrio-ventricular grooves
- Posterior left ventricular branch and posterior descending coronary artery after the division.
- Supplies the posterior and inferior wall of the left ventricle and posterior third of interventricular septum as well as the posteriormedial papillary muscle in the left ventricle

Coronary artery dominance

- The artery which crosses the crux is defined as the dominant coronary artery.
- Right coronary dominance is much more common than left dominance.
- However, the major portion of left ventricular myocardium is supplied by the left coronary artery.

Left coronary artery



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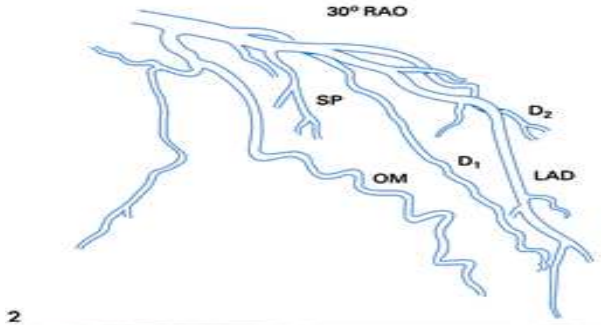

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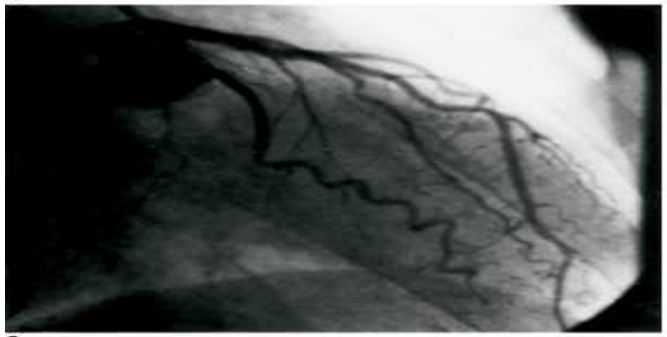


3

A

Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

From King SB, Douglas JS, Morris DC. New angiographic views for coronary arteriography. In Hurst JW, ed. *The Heart, Update IV.* New York: McGraw-Hill, 1980:275–287. Reproduced with permission from the publisher, editor, and authors.

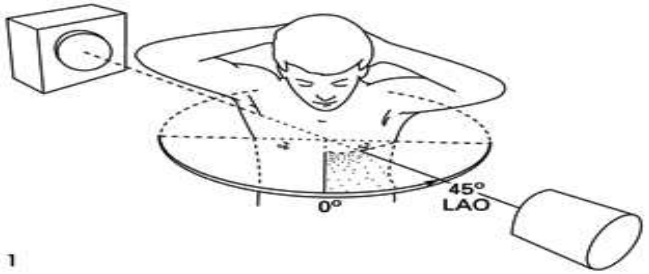
Fig. 17-7 Accessed 04/01/2010

Right anterior oblique view

Right coronary artery

From King SB, Douglas JS, Morris DC. New angiographic views for coronary arteriography. In Hurst JW, ed. *The Heart, Update IV.* New York: McGraw-Hill, 1980:275–287. Reproduced with permission from the publisher, editor, and authors.

Fig. 17-8 Accessed 04/01/2010



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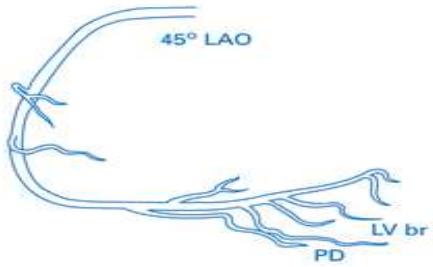

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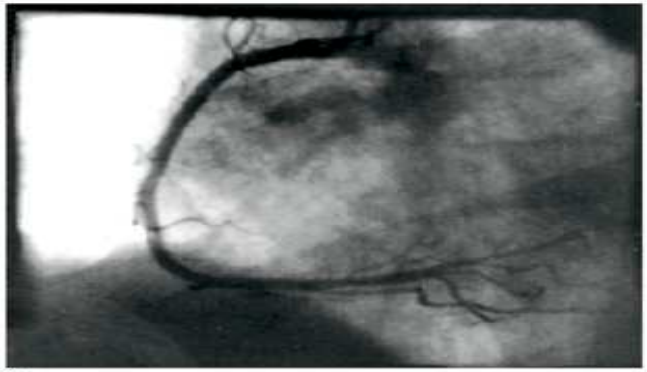
Left anterior oblique view



3

A

Infarction

- Left anterior descending coronary artery (40% to 50%) infarcts involve the anterior wall of left ventricle near the apex; the anterior portion of ventricular septum; and the apex circumferentially
- Left circumflex coronary artery (15% to 20%) infarcts involve the lateral wall of left ventricle except at the apex

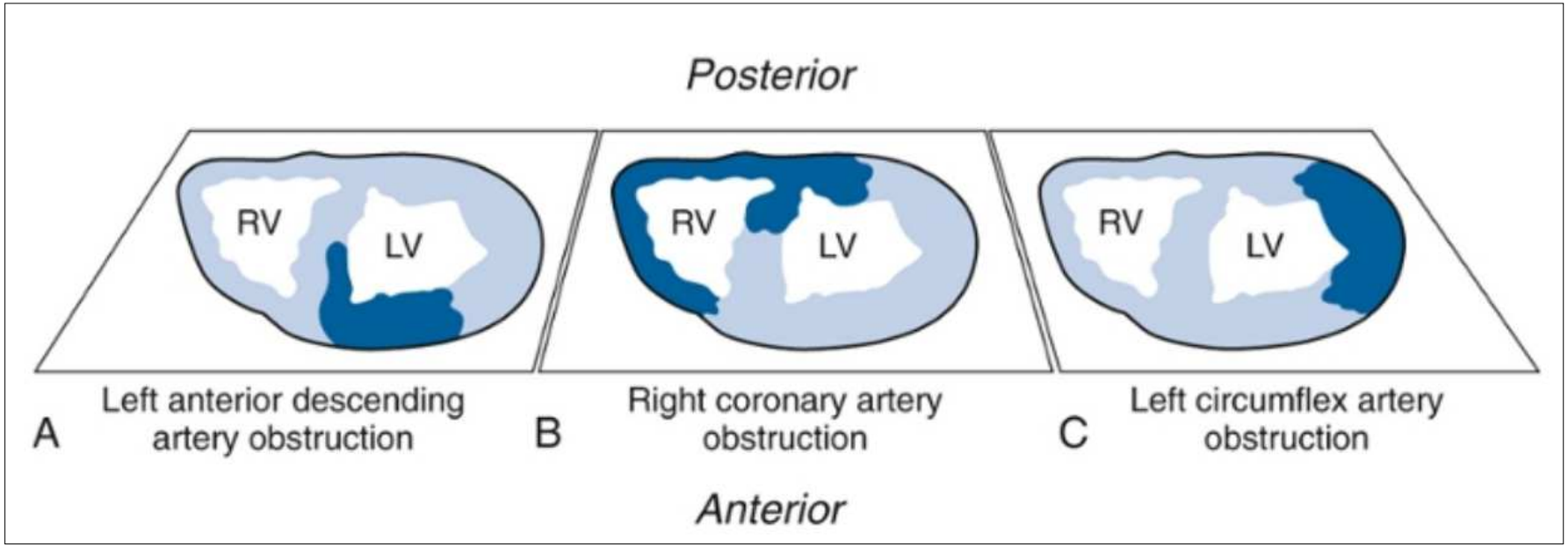
Infarction

- Right coronary artery (30% to 40%) infarcts involve the inferior/posterior wall of left ventricle; posterior portion of ventricular septum; and the inferior/posterior right ventricular free wall in some cases
- Isolated infarction of the right ventricle is unusual (only 1% to 3% of cases), as is infarction of the atria.

Infarction

- Of MIs caused by a right coronary obstruction, 15% to 30% extend from the posterior free wall of the septal portion of the left ventricle into the adjacent right ventricular wall.
- Isolated infarction of the right ventricle is unusual (only 1% to 3% of cases), as is infarction of the atria.

Coronary artery distribution



Pathophysiology of ischemia

- For any given level of a demand for O_2, the myocardium will control the supply of oxygen-rich blood to prevent under-perfusion of myocytes
- The major determinants of myocardial 0_2 demand (MVO_2) are heart rate, myocardial contractility, and myocardial wall tension (stress)
- Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole.
- Blood flows from the epicardium to the endocardium
- Subendocardium most vulnerable to hypoxic injury

Pathophysiology of ischemia

- Major resistance vessels are prearteriolar and arteriolar or intramyocardial capillary vessels
- Intramyocardial vessels have great capacity for dilatation (autoregulation)
- With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels dilate to reduce vascular resistance and maintain coronary blood flow.
- A pressure gradient develops across the proximal stenosis, and post-stenotic pressure falls.

Pathophysiology of ischemia

- When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction
- Ischemia is precipitated by increased MVO_2
- Tachycardia and aortic valve disease interfere with coronary artery filling
- O_2 depletion leads to increased anerobic glycolysis to maintain ATP levels.
- In liver and muscle, glycogen is depleted to generate glucose.
- Lactic acid production increases.

Pathophysiology of ischemia

- As ATP needs are greater with enhanced contractility in the compensating heart, the end result is lowering of ATP stores and diminished contractility with development of failure
- ATP depletion by 5-10% (failure of Na^+-K^+-ATPase) leads to entry of Na^+ into cell, K^+ efflux, cell swelling, and dilation of endoplasmic reticulum with detachment of ribosomes and dissociation of polysomes with resultant decline in protein synthesis.
- Misfolded proteins trigger a response leading to cell death.

Pathophysiology of ischemia

- With decompensation, Ca^{2+}-ATPase leads to elevated levels of intracellular Ca^{2}.
- In the mitochondrion, activation of phospholipase and sphingomyelin pathways
- Generation of breakdown products such as free fatty acids and ceramide are seen.
- High conductance ion channels are opened on the inner membrane
- Cytochrome c leaks into cytosol.
- ATP generation falls.
- Apoptosis triggered.

Ischemia

- Reactive oxygen species are generated (affecting gene integrity).
- Ischemia causes functional disturbances of the heart, including:
- Impaired relaxation.
- Occurs first, causing diastolic dysfunction.
- Impaired contraction.
- Occurs second, causing systolic dysfunction.
- Heart muscle contraction stops within 60 seconds of occlusion.
- Injury not reversible after 30 minutes of interruption of blood flow.

Histopathology

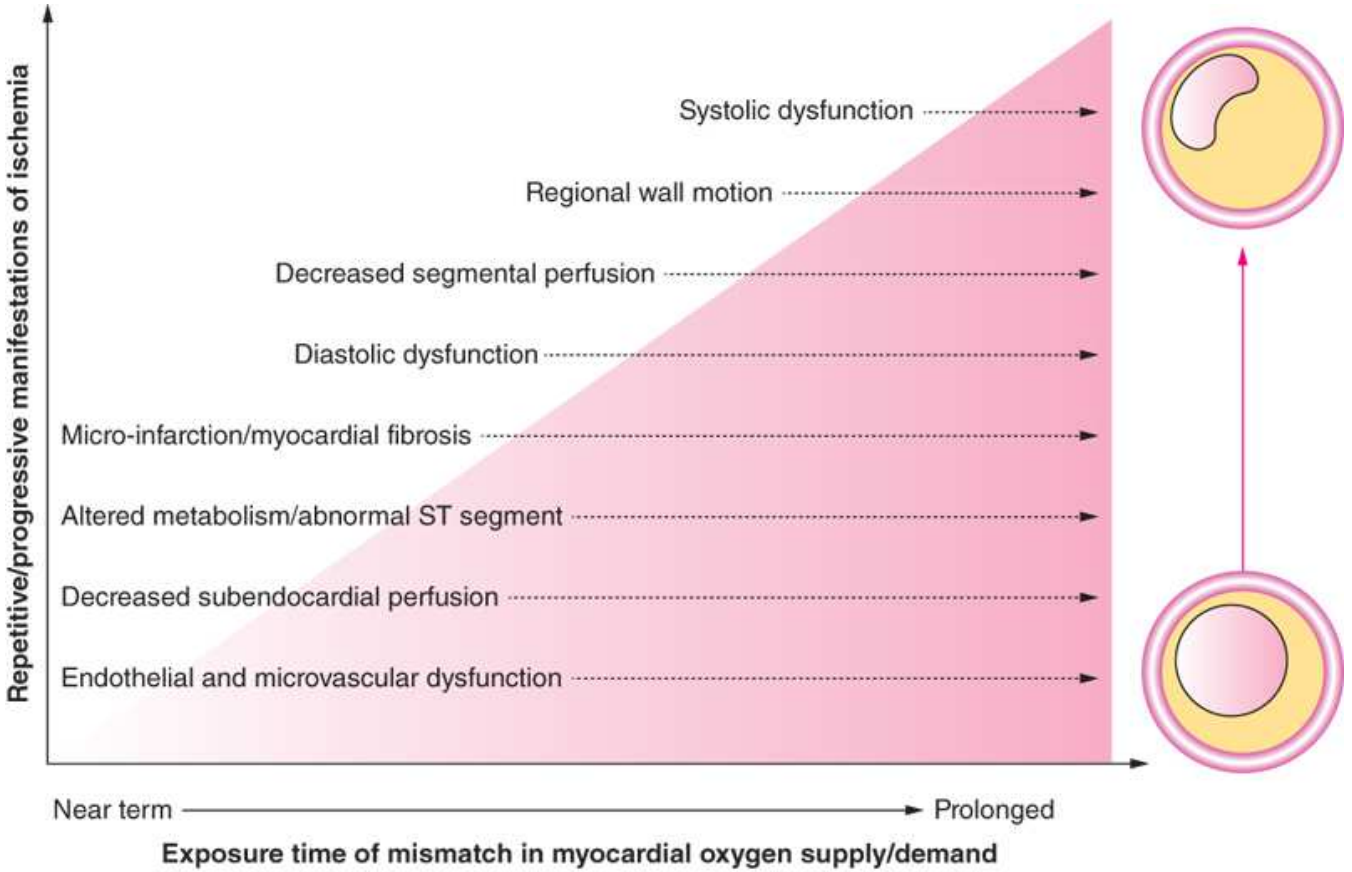
- An apoptotic cell is reduced in size and the nuclear chromatin is fragmented.
- The cell membrane is intact.
- Intracellular contents may be released as apoptotic bodies.
- No inflammatory response is induced by the dying cell.
- The dying cell is enlarged and the nucleus is pyknotic.
- If the cell membrane is disrupted,
- Lysoszymes released.
- Enzymes leak out of the cell, triggering an inflammatory response.

Consequences of ischemia

- Myocardial stunning
- A prolonged (hours to days) but reversible dysfunction after an acute ischemic event.
- Microvascular damage has occurred, however

Consequences of ischemia

- Myocardial hibernation
- Occurs when oxygenation is adequate to maintain viability of the myocardium but cannot support normal function.
- Death of myocardial cells.
- A limiting toxicity of anthracycline, taxane, cyclophosphamide, fluorouracil, and trastuzumab use is myocardial toxicity.
- Major adverse cardiac events can be predicted by response to reactive hyperemia (endothelial peripheral arterial tonometry).



Cascade of mechanisms and manifestations of ischemia.(Modified from LJ Shaw et al: J Am Coll Cardiol 54:1561, 2009. Original figure illustration by Rob Flewell.)

Angina

- Substernal chest pressure described as “crushing” or “burning” that may radiate to the left jaw, either shoulder or arm.
- A clutched fist over the sternum may be displayed spontaneously when describing the pain (Levine’s sign)
- “Indigestion” often used as a descriptor by patient

- Women often complain of burning pain, tenderness.
- Worsens with activity and is relieved with rest.
- Of short duration (no longer than 15 minutes)
- Recurrent

Angina

- Changes are brought on by exertion, eating, emotional stress
- EKG demonstrates ST segment depression while the patient is symptomatic.
- Any non-musculoskeletal symptom that reliably recurs with exertion should raise the suspicion of angina.

Angina

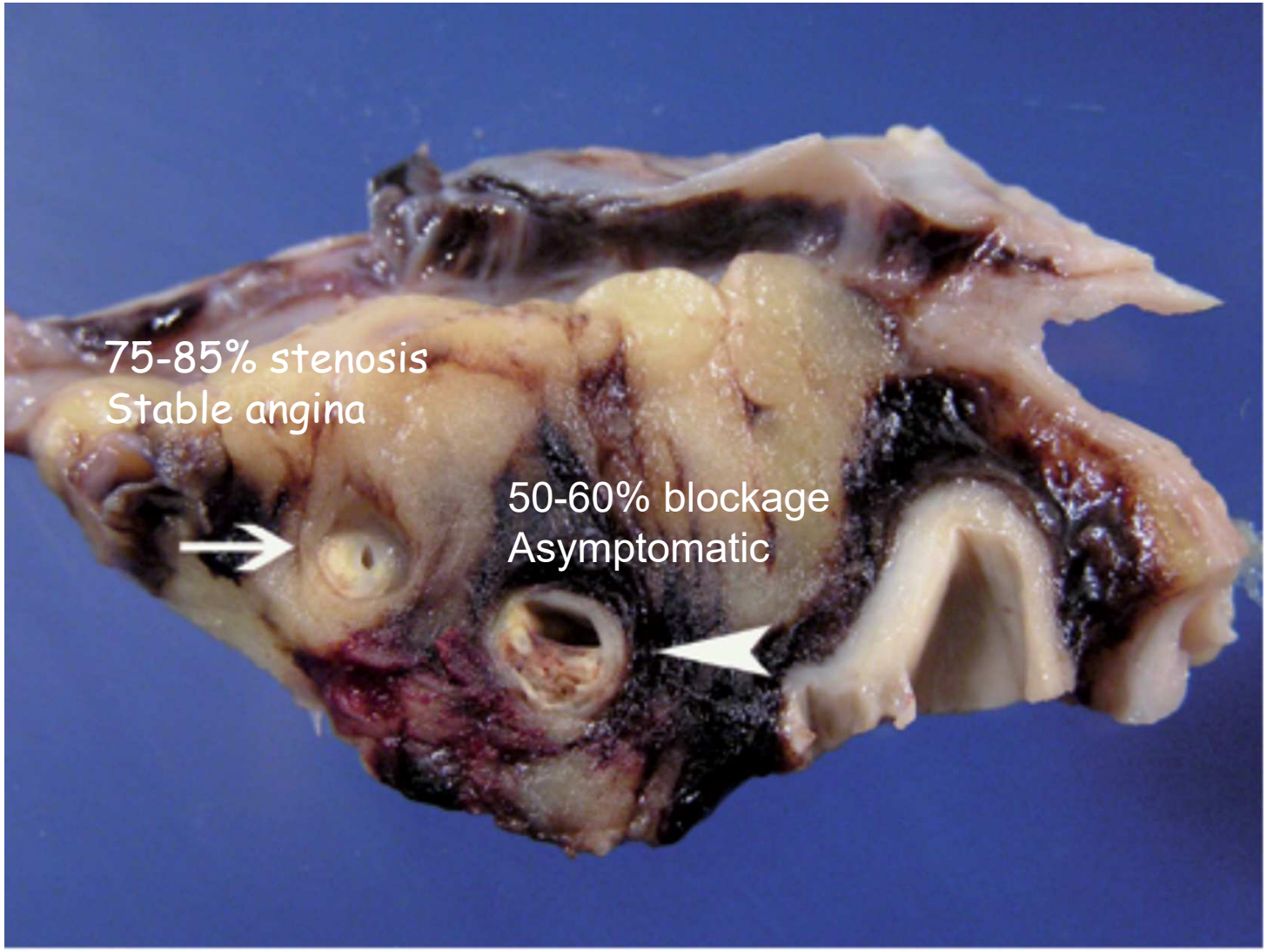
- Men >50 and women >60 years of age who present with typical symptoms of angina have a likelihood of over 90% of having coronary artery disease.
- Stress testing useful in evaluating patients with stable angina. (LR+, 2.5 for exercise; LR+, 6.9 if vasodilator employed with exercise)
- Response to nitroglycerin does not differentiate angina from esophageal pain.

Angina

- In stable disease there is a stable atherosclerotic plaque limiting blood flow to the heart.
- Unstable disease (crescendo or pre-infarction angina)
- Symptoms occur at rest or are increased in frequency or severity.
- Due to thrombus formation on a plaque, further limiting blood flow
- Multiple coronary arteries with >90% occlusion
- Both produce subendocardial ischemia
- Unstable angina is not associated with CK or Troponin I elevations following chest pain

Anti-anginal therapy

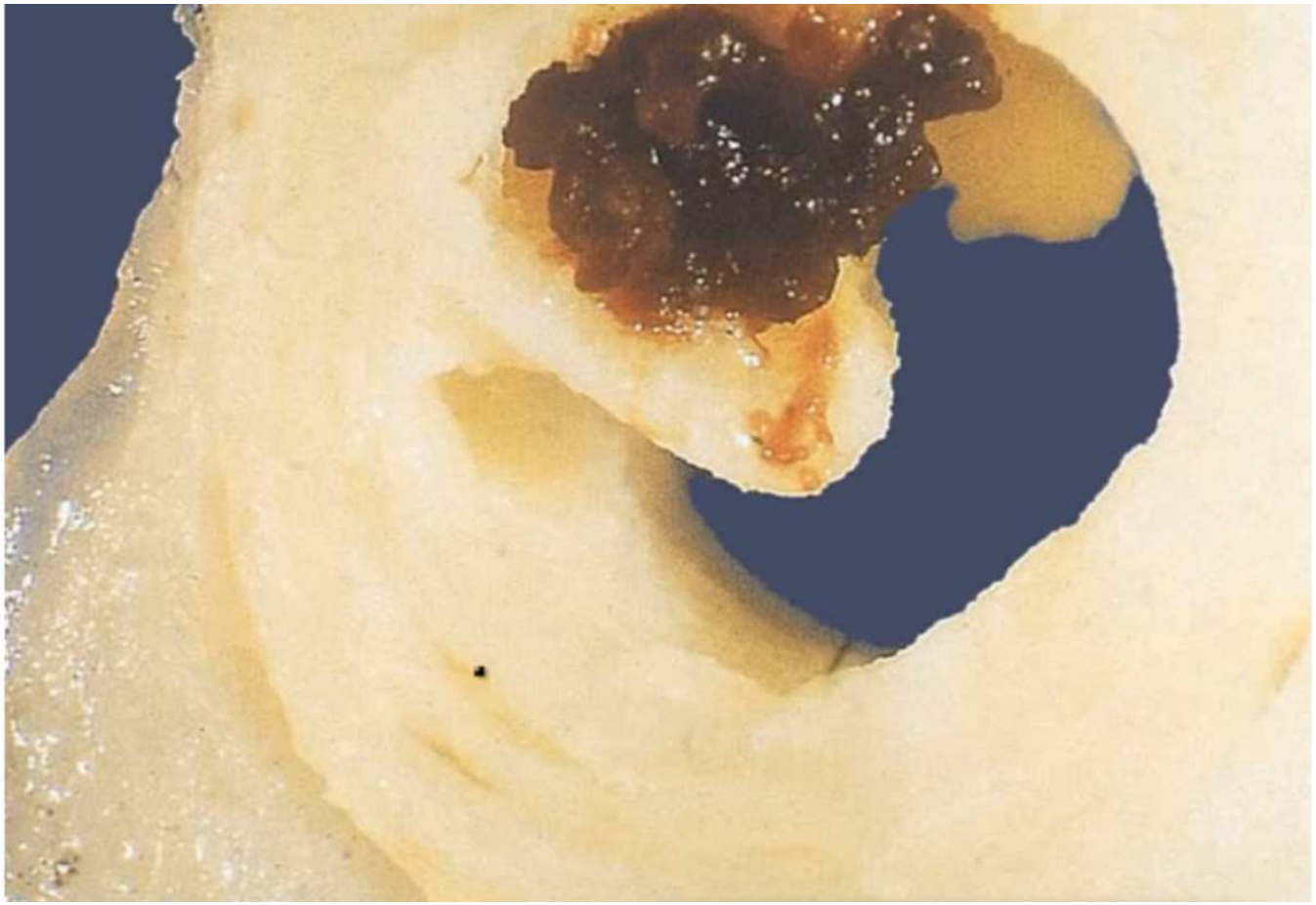
Pharmacologic agent	Mechanism of action	Indications
Nitroglycerin (short acting nitrate); Isosorbide dinitrate (long acting nitrate)	Nitric oxide release leads to vasodilatation	Stable, unstable, and variant angina
Propanolol; Atenolol, metoprolol	Non-selective β-blockers and β1-selective blockers reduce Oxygen demand by affecting heart rate and contractility	Stable angina
Nifedipine	Blocks L-type Calcium channel promoting vasodilatation	Variant angina
Diltiazem If used with β-blocker, may depress myocardium	Reduce Oxygen demand by affecting heart rate and contractility	Stable angina



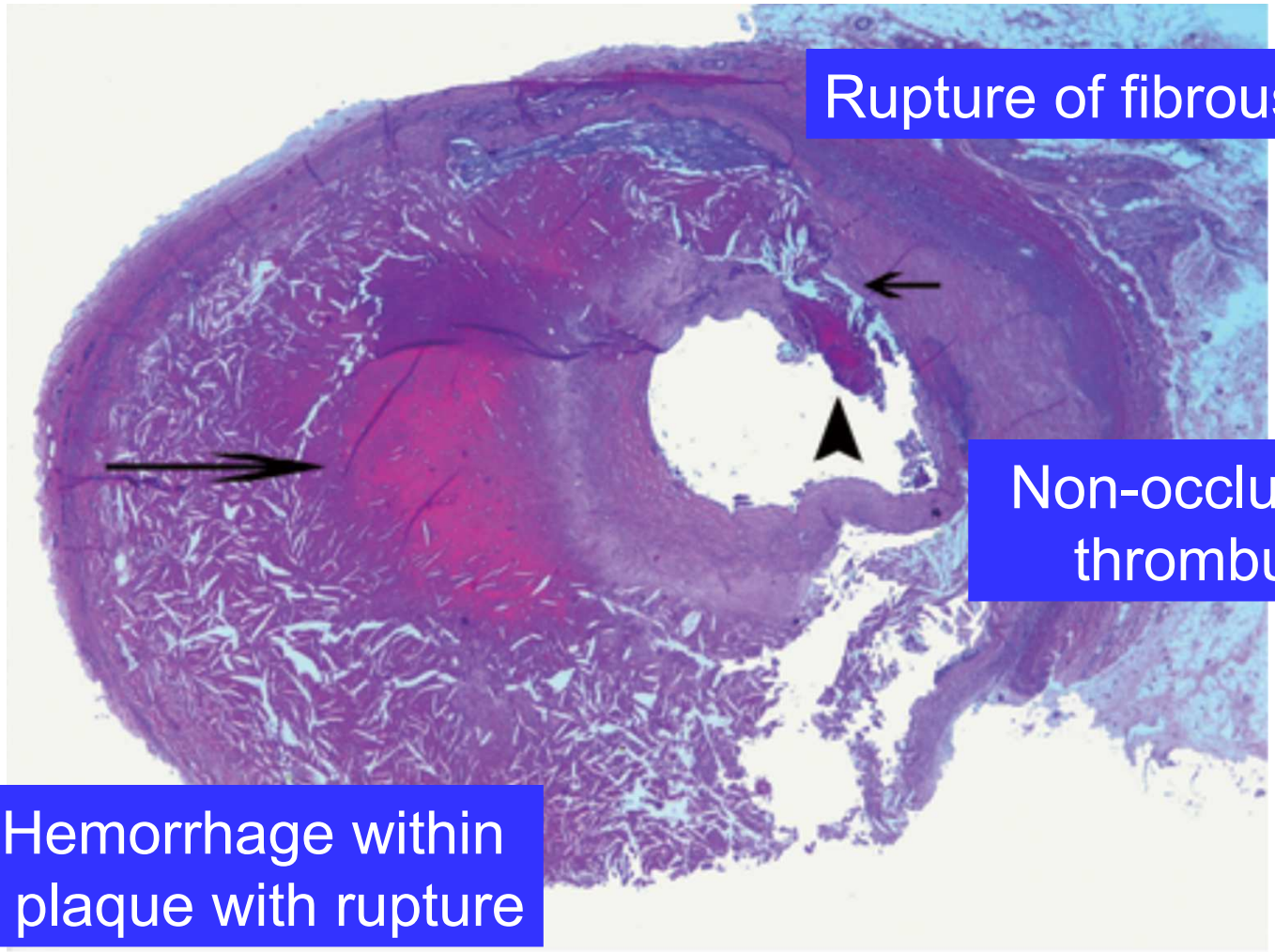
Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

Fig. 10-5

Thrombus on atherosclerotic plaque



Sheppard, MN, Herrington, CS, “The Cardiovascular System,” in Herrington, CS (ed), Muir’s Textbook of Pathology, 15th edition. 2014. CRC Press. Boca Raton, Florida. Fig. 6-41



Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

Fig. 10-7

Prinzmetal's angina

- Due to vasospasm and is unrelated to activity.
- Episodic
- May occur at rest or during midnight to morning hours
- Generally 50-60 years of age
- ST elevation is demonstrated when symptomatic.
- Thromboxane A_2 as cause
- Usually reflect spasm near an area of stenosis

Prinzmetal's angina

- Resolves spontaneously or with nitroglycerin.
- Managed with dihydropyridine calcium channel blockers.
- May precipitate with ergonovine as challenge test
- Ergot alkaloid that stimulates α-adrenergic and serotonergic receptors in smooth muscle and leads to vasoconstriction
- ASA increases severity of ischemic episode

Chest pain

- Pleuritic chest pain, stabbing chest pain, postional chest pain, and chest pain reported by palpation are unlikely to be associated with myocardial infarction (LR-, 0.2).

Chest pain

- Chest pain radiating to both arms (LR+, 9.7; LR- 0.6) or to right arm (LR+, 7.3; LR-, 0.6) are associated with more diffuse myocardial injury.
- Left arm pain has but an LR+ of 2.2 for myocardial injury.
- The presence of an S_3 on auscultation has an LR+ of 2.9.
- Response to nitroglycerin does not distinguish those patients with myocardial infarction from those who do not.

Chest pain

- The Goldman chest pain decision rule relies on ST segment elevation (LR+, 11) or pathologic Q waves (LR+, 3.9) to define those at high risk for an acute myocardial infarction;
- T-wave peaking or inversion (LR+, 3.1), any conduction defect (LR+, 2.7), or ST-segment depression (LR+, 3.2) to define those with evidence of acute ischemia;
- And further uses the findings of râles, and hypotension for stratification of risk to permit intelligent triage.

Table 12.4 Approximate Time of Onset of Key Events in Ischemic Cardiac Myocytes

Feature	Time
Onset of ATP depletion	Seconds
Loss of contractility	<2 minutes
ATP reduced	
to 50% of normal	10 minutes
to 10% of normal	40 minutes
Irreversible cell injury	20–40 minutes
Microvascular injury	>1 hour

ATP, Adenosine triphosphate.

Table 1. Tests to Diagnose and Assess the Prognosis of Clinically Significant Coronary Disease.*

Test	Sensitivity	Specificity	Provides Prognostic Information†	Considerations
	percent			
Exercise stress test				
ECG	45–50	85–90	Yes	Easy to perform; can be used only with normal baseline ECG findings
Echocardiography	80–85	80–88	Yes	Cannot be used in patients with left bundle-branch block or right bundle-branch block; interpretation may be limited in overweight patients
Nuclear test	73–92	63–87	Yes	Radiation exposure
Pharmacologic stress test				
Dobutamine				
Echocardiography	79–83	82–86	Yes	Limited to patients who cannot exercise; can induce arrhythmias
MRI	79–88	81–91	Yes	Limited use in overweight patients and those with metal implants; can induce arrhythmias
Adenosine				
Echocardiography	72–79	92–95	Yes	Cannot be used in patients with left bundle-branch block or right bundle-branch block; interpretation may be limited in overweight patients; can cause wheezing and heart block
Nuclear test	90–91	75–84	Yes	Radiation exposure; can cause wheezing and heart block
MRI	67–94	61–85	Yes	Limited use in overweight patients and those with metal implants; can cause wheezing and heart block
PET	81–-97	74–91	No	Limited availability; can cause wheezing and heart block

* Modified from Montalescot et al.[9] ECG denotes electrocardiography, MRI magnetic resonance imaging, and PET positron-emission tomography.
† Most tests evaluate the risk of death, myocardial infarction, or both to assess prognosis.

Stress testing

- An exercise stress test to maximum performance may not demonstrate abnormality in patients with collateral circulation
- With exercise, systemic pressure rises, increasing coronary blood flow.
- The use of adenosine or dipyrimadole may precipitate symptoms
- The administration of a coronary vasodilator, however, is not associated with a rise in aortic pressure as in exercise, and blood flow is favored in larger vessels.
- Thus, there is a “steal” from small collaterals, leading to ischemia.

Therapeutic strategy

- Early treatment with t-PA (within 3 hours of onset of symptoms) is associated with better outcomes.
- Tenecteplase is drug of choice to promote clot lysis in both acute myocardial infarction and acute stroke.
- Protects ischemic tissue
- IV bolus (ateplase is given by infusion)
- Increased hemorrhagic risk compared to ateplase

Intervention

- Thrombolytic therapy not as effective as percutaneous intervention.
- Contraindicated if recent surgery or active bleeding
- Angiography if invasive therapy required.
- In those patients with single vessel disease, there is no difference in mortality between percutaneous intervention (and stenting) and medical management.
- Better symptom relief with percutaneous intervention; however, must be repeated frequently.

Intervention

- With balloon PTCA, 15% obstructed within 6 months
- Bare metal or drug eluting stents have longer patency but are associated with thrombosis
- Drug eluting stent coated with paclitaxel (taxane)
- If multi-vessel disease or disease of the left main coronary artery or the proximal left anterior descending coronary artery, coronary artery bypass grafting has a clear survival benefit, particularly in diabetic patients.
- Internal mammary artery graft has better survival than graft with saphenous veins

Cardiac function

- Increased left ventricle filling pressure: radiographic redistribution, jugular venous distention (LR+, 5), or S_3 (LR+, 11).
- If no râles, jugular venous distention, S3, or radiographic change, filling pressure is not elevated.
- Prevalence of increased filling pressure is 22% if no known severe systolic dysfunction
- If known systolic dysfunction, one finding alone suggests low filling pressure (73% prevalence, >90% probability).

Cardiac function

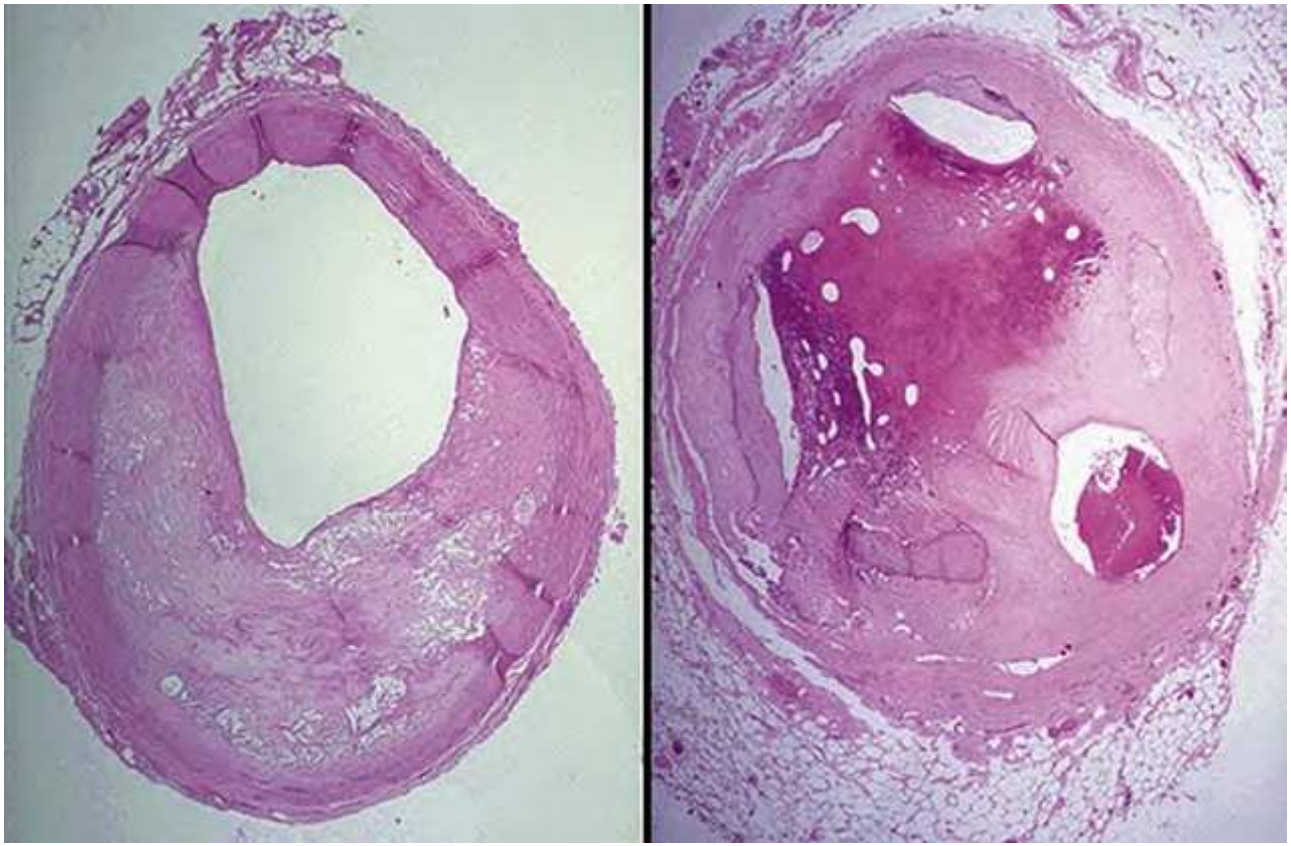
- Ejection fraction <40% is usually associated with tachycardia and a systolic blood pressure <90 mmHg.
- Anterior Q waves or the presence of a left bundle branch block have a sensitivity 90% for diminished ejection fraction.
- The presence of more than 3 of the following findings are associated with a 90% probability of low ejection fraction:
- Radiographic cardiomegaly, abnormal apical impulse, abnormal anterior Q waves, and left bundle branch block
- Diastolic dysfunction: BP >160/100

Mechanism of infarction

- A coronary artery atheromatous plaque undergoes an acute change consisting of intraplaque hemorrhage, erosion or ulceration, or rupture or fissuring.
- Coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap
- Exposure to subendothelial collagen and necrotic plaque contents leads to platelet adhesion, activation, and aggregation.
- Microthrombi form.

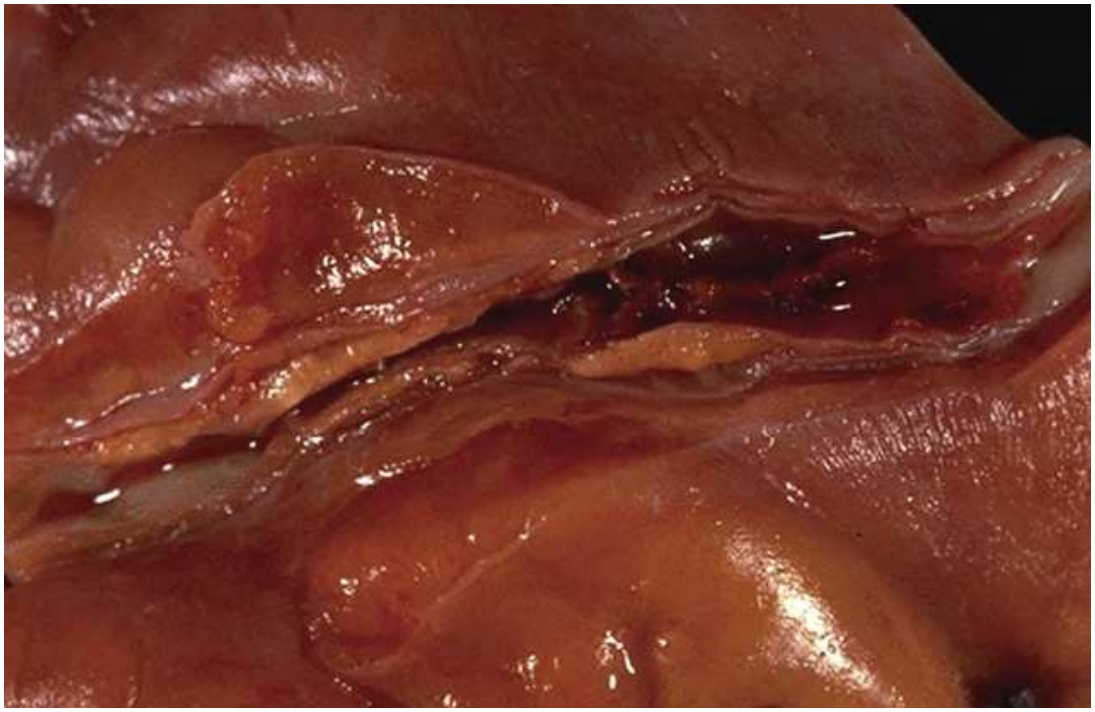
Mechanism of infarction

- Vasospasm is stimulated by mediators released from platelets
- Thromobxane A2
- Tissue factor activates the coagulation pathway, adding to the bulk of the thrombus.
- Within minutes, the thrombus can expand to completely occlude the vessel lumen.
- Subendocardium most vulnerable
- Within 2-3 hours, 50% of wall thickness involved
- At 6 hours, the lesion is transmural



Left. The coronary artery is narrowed by 60% to 70%. Probably asymptomatic. Right: The coronary artery has even more severe occlusion, with evidence for previous thrombosis and organization of the thrombus leading to recanalization.

Sheppard, MN, Herrington, CS, "The Cardiovascular System," in Herrington, CS (ed), Muir's Textbook of Pathology, 15th edition. 2014. CRC Press. Boca Raton, Florida. Fig. 2.26



Coronary thrombosis. Thickened arterial walls with yellow-tan plaques that narrow the arterial lumen, is thrombosis. The dark red thrombus occludes this anterior descending coronary artery, opened longitudinally.

Sheppard, MN, Herrington, CS, "The Cardiovascular System," in Herrington, CS (ed), Muir's Textbook of Pathology, 15th edition. 2014. CRC Press. Boca Raton, Florida. Fig. 1.61

Figure 2-27

Infarction

- Coronary thrombosis is present in 90% of infarct patients at 4 hours post-onset of chest pain as demonstrated by angiography.
- At 12 hours, thrombosis can be demonstrated in only 60% of infarct patients
- 10% of transmural infarcts may be due to vasospasm or drug use

Infarction

- A transmural or STEMI infarct occurs because of complete occlusion of the coronary vessel by a thrombus.
- ST elevation on EKG
- Q waves will be present on the EKG.
- CKMB and Troponin I levels elevated.

Infarction

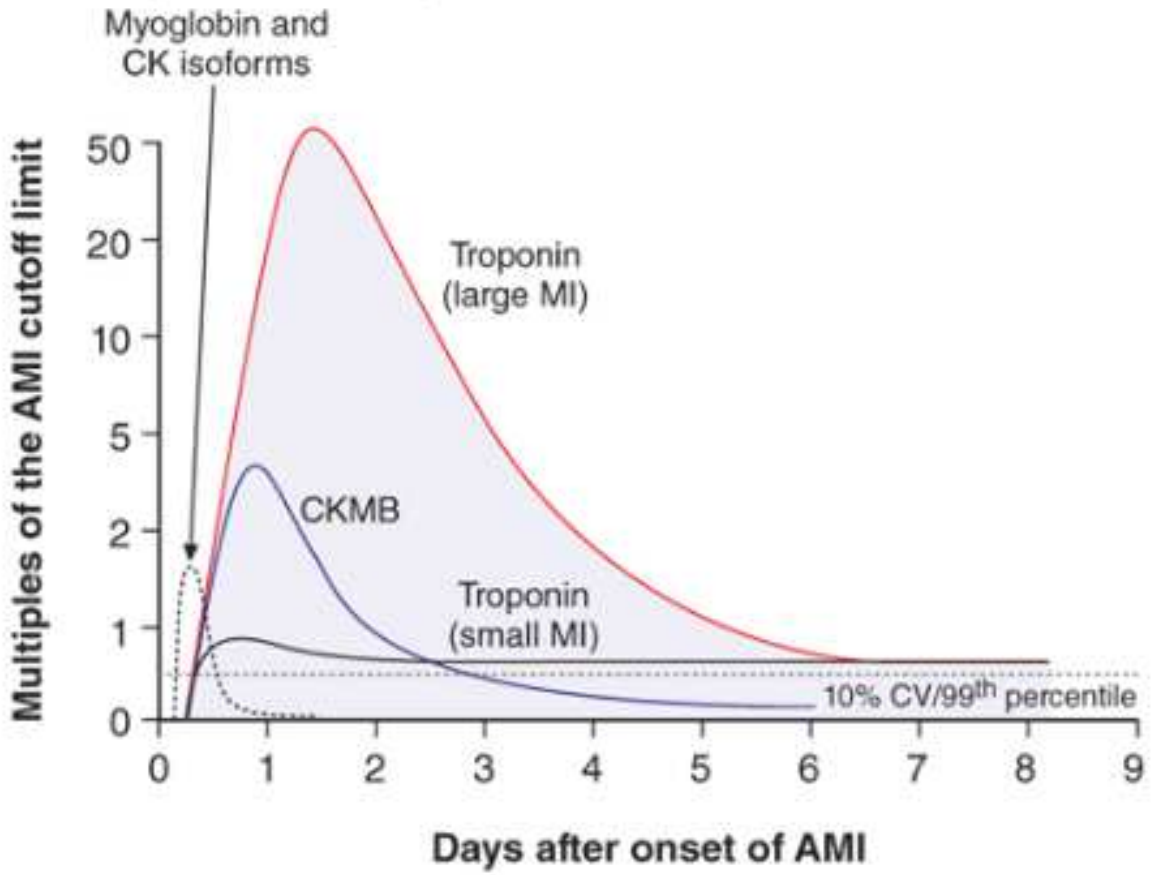
- If the thrombus lyses before 2-4 hours, a subendocardial or NSTEMI infarct results.
- A NSTEMI infarct may also occur if there is a sudden change in the plaque which significantly and rapidly narrows the lumen (to >70% stenosis) but does not completely occlude it (or if there is poor perfusion as in shock).
- ST depression noted on EKG
- No Q waves on EKG
- NSTEMI infarct will show enzyme elevations.

Infarction

- 10% have stenosis of the left main coronary artery
- 35% have three-vessel disease
- 20% have two-vessel disease
- 20% have single-vessel disease
- 15% have no obvious disease
- May involve microcirculation
- May be related to vasospasm

Cardiac enzymes

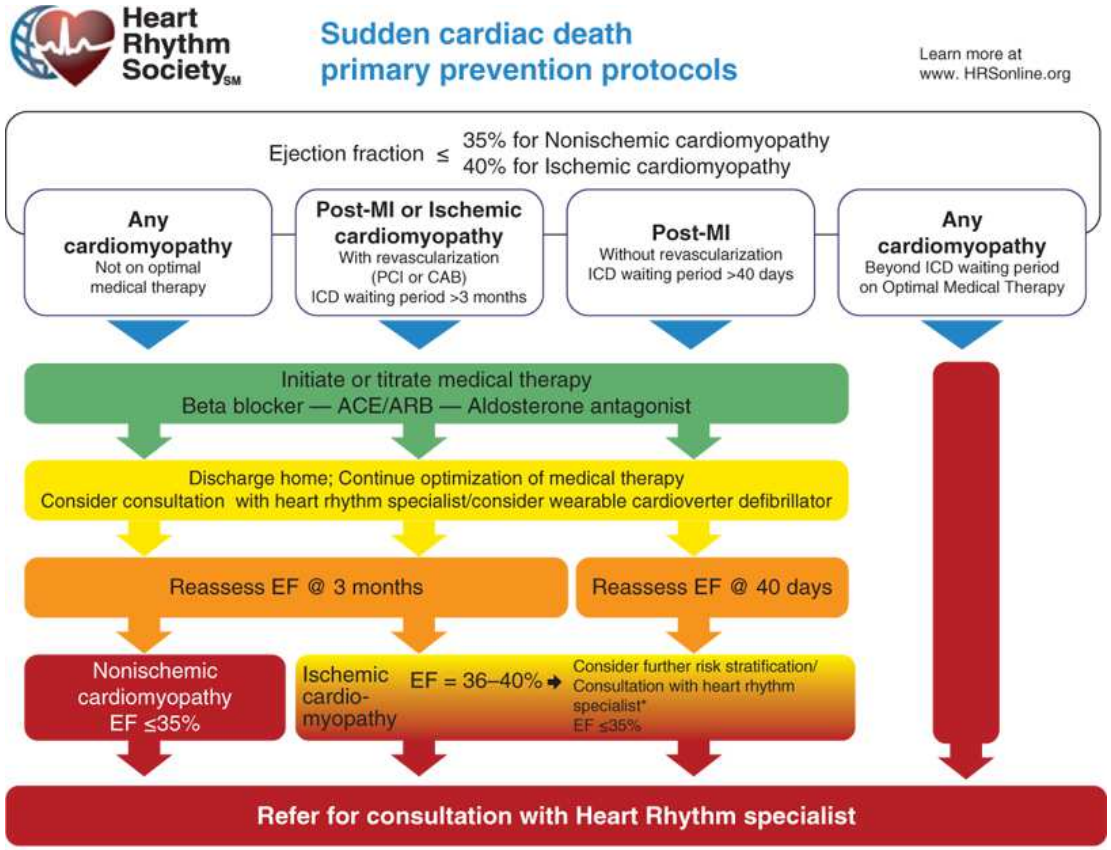
- Time to elevation is 3-12 hrs
- CK-MB and cTnI peak at 24 hours
- CK-MB returns to normal in 48-72 hrs, cTnI in 5-10 days,
- cTnT in 5 to 14 days
- LDH (isozymes 1-3) is also elevated with injury



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Sudden death

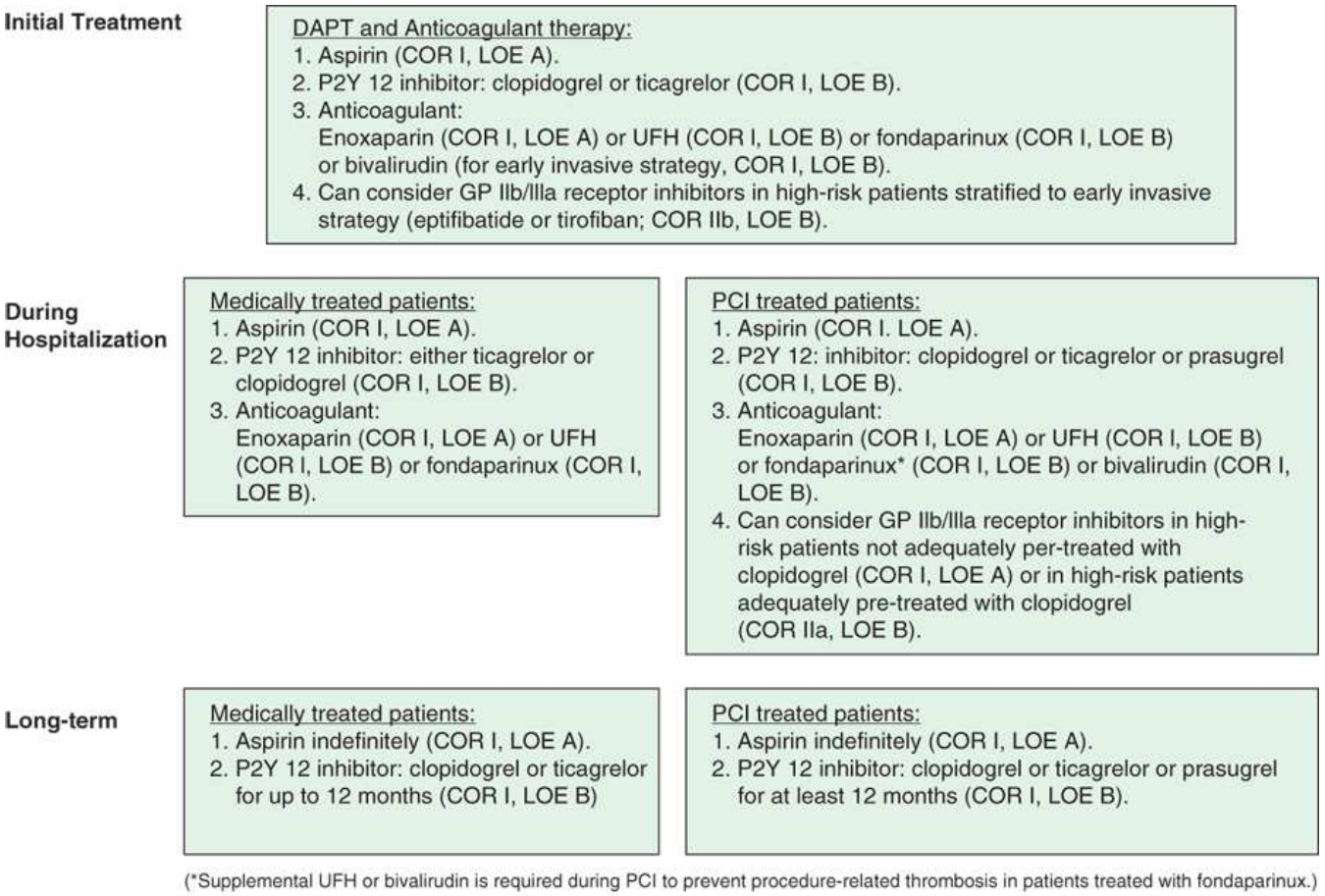
- The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms
- Over half occur in the first hour.
- 80% do no have an occlusive thrombus nor evidence of a recent infarction
- Hyperthermia improves survival and neurologic outcome after cardiac arrest, particularly if preceded by ventricular tachycardia or fibrillation



Algorithm for assessment of need for implantation of a cardioverter-defibrillator. The appropriate management is selected based on measurement of left ventricular ejection fraction, the timing following infarction, and whether revascularization has been performed. (Reproduced from data at www.hrsonline.org.)

Complications of infarction

- Left and right ventricular failure (cardiogenic shock)
- Conduction abnormalities, arrhythmias
- Left ventricular wall aneurysm or rupture in 3-5%
- 5-10% involve posterior-inferior or lateral wall
- Extension of the infarct to involve the right ventricle (an inferior infarction will extend to involve the right ventricle in 20% of cases; though there will be elevated jugular venous pressure, the lungs will be clear).
- Pericarditis
- Mural thrombus



Antiplatelet and anticoagulation treatment summary for NSTE-ACS according to the 2014 American Heart Association/American College of Cardiology Practice Guideline. COR, classes of recommendation; DAPT, dual antiplatelet therapy; GP IIb/IIIa, glycoprotein IIb/IIIa; LOE, levels of evidence; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. (From A Eisen, RP Giugliano: Cardiol Rev 24;170, 2016.)

Table 12-4 Approximate Time of Onset of Key Events in Ischemic Cardiac Myocytes

Feature	Time
Onset of ATP depletion	Seconds
Loss of contractility	<2 min
ATP reduced	
to 50% of normal	10 min
to 10% of normal	40 min
Irreversible cell injury	20-40 min
Microvascular injury	>1 hr

ATP, Adenosine triphosphate.

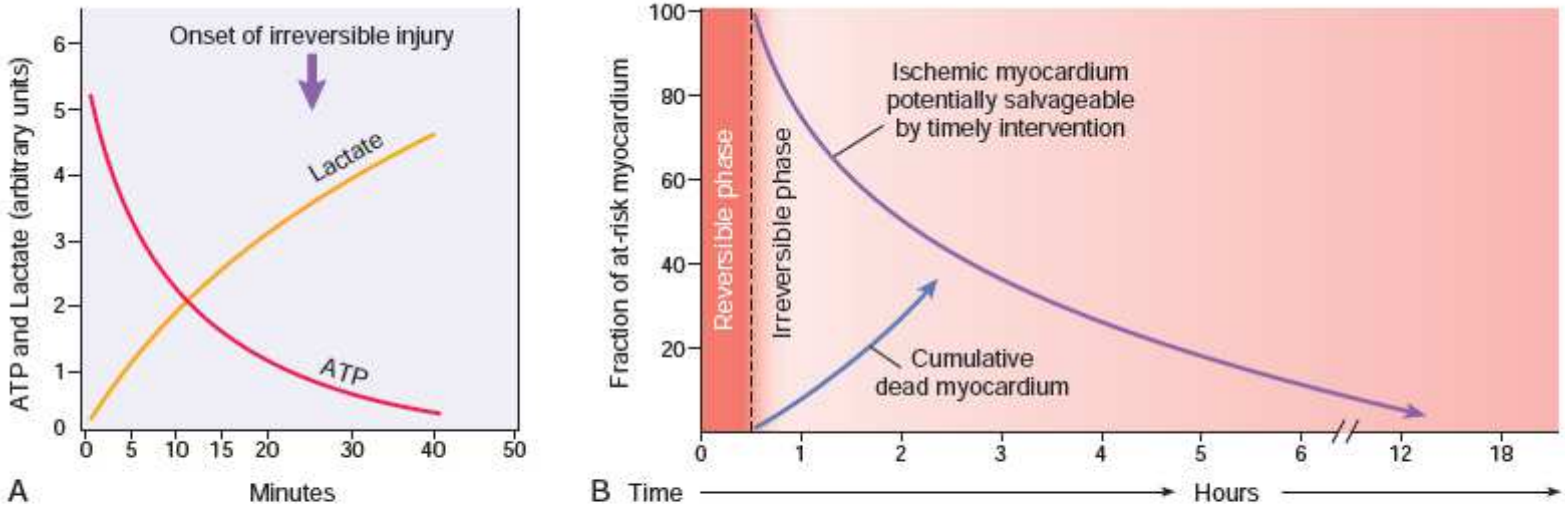


Figure 12-10 Temporal sequence of early biochemical findings and progression of necrosis after onset of severe myocardial ischemia. **A,** Early changes include loss of adenosine triphosphate (ATP) and accumulation of lactate. **B,** For approximately 30 minutes after the onset of even the most severe ischemia, myocardial injury is potentially reversible. Thereafter, progressive loss of viability occurs that is complete by 6 to 12 hours. The benefits of reperfusion are greatest when it is achieved early, and are progressively lost when reperfusion is delayed. (Modified with permission from Antman E: Acute myocardial infarction. In Braunwald E, et al [eds]: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed. Philadelphia, WB Saunders, 2001, pp 1114-1231.)

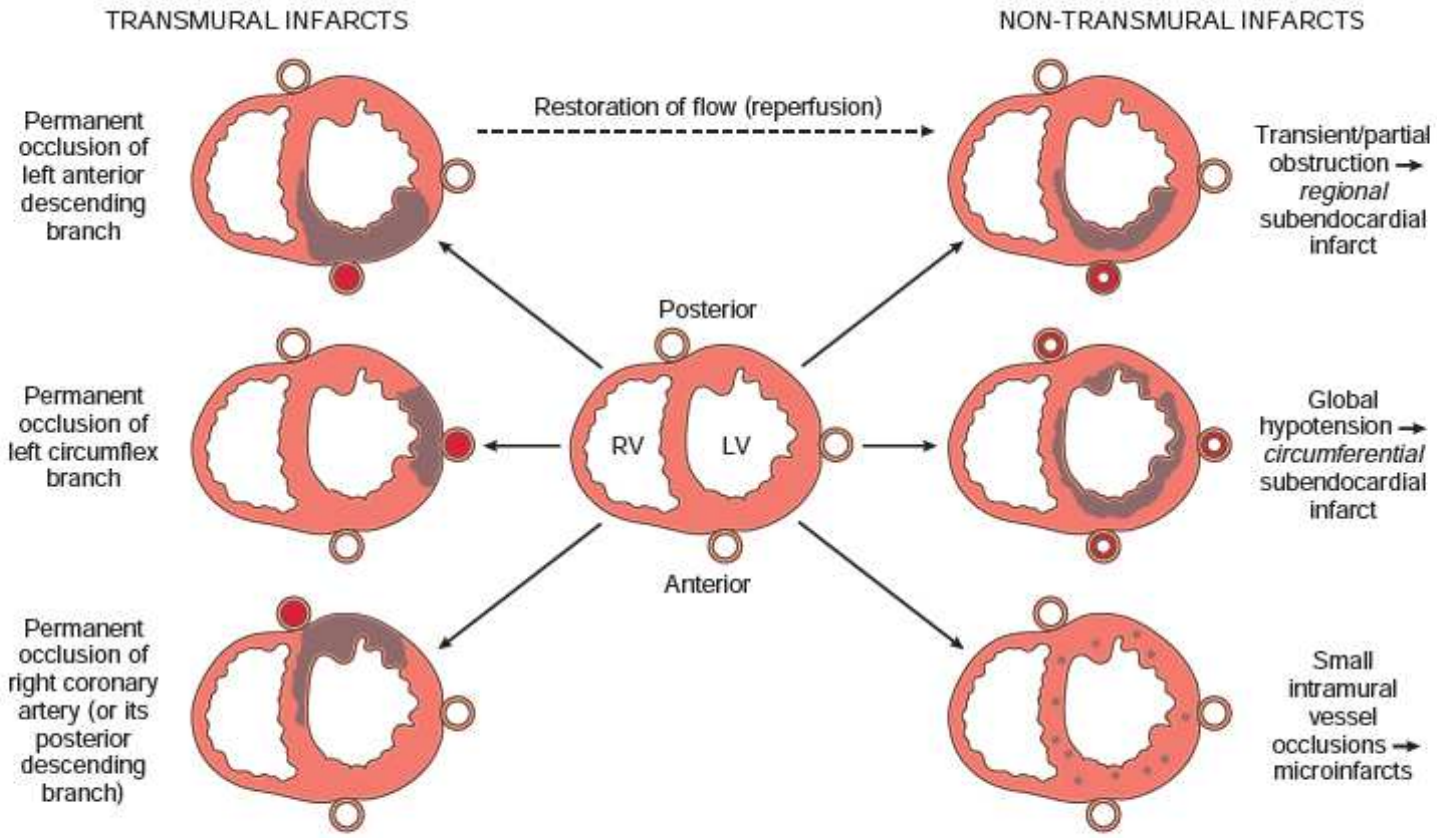


Figure 12-12 Distribution of myocardial ischemic necrosis correlates with the location and nature of decreased perfusion. *Left,* The positions of transmural acute infarcts resulting from occlusions of the major coronary arteries; *top to bottom,* left anterior descending, left circumflex, and right coronary arteries. *Right,* The types of infarcts that result from a partial or transient occlusion, global hypotension, or intramural small vessel occlusions.

Schoen, F and Mitchell, RN, "The Heart," in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

Table 12-5 Evolution of Morphologic Changes in Myocardial Infarction

Time	Gross Features	Light Microscope	Electron Microscope
Reversible Injury			
0-½ hr	None	None	Relaxation of myofibrils; glycogen loss; mitochondrial swelling
Irreversible Injury			
½-4 hr	None	Usually none; variable waviness of fibers at border	Sarcolemmal disruption; mitochondrial amorphous densities
4-12 hr	Dark mottling (occasional)	Early coagulation necrosis; edema; hemorrhage	
12-24 hr	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; early neutrophilic infiltrate	
1-3 days	Mottling with yellow-tan infarct center	Coagulation necrosis, with loss of nuclei and striations; brisk interstitial infiltrate of neutrophils	
3-7 days	Hyperemic border; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border	
7-10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; granulation tissue at margins	
10-14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition	
2-8 wk	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity	
>2 mo	Scarring complete	Dense collagenous scar	

Schoen, F and Mitchell, RN, "The Heart," in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

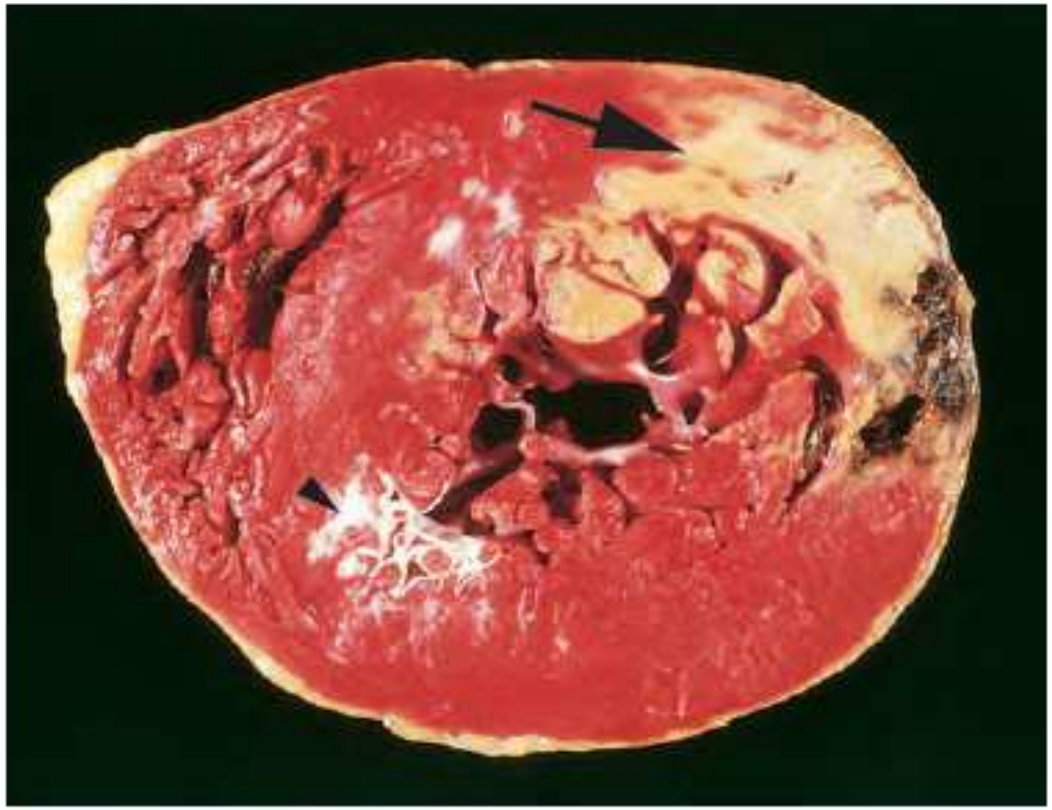


Figure 12-13 Acute myocardial infarct, predominantly of the posterolateral left ventricle, demonstrated histochemically by a lack of staining by triphenyltetrazolium chloride in areas of necrosis *(arrow)*. The staining defect is due to the lactate dehydrogenase leakage that follows cell death. Note the myocardial hemorrhage at one edge of the infarct that was associated with cardiac rupture, and the anterior scar *(arrowhead)*, indicative of old infarct. Specimen is oriented with the posterior wall at the top.

Schoen, F and Mitchell, RN, "The Heart," in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

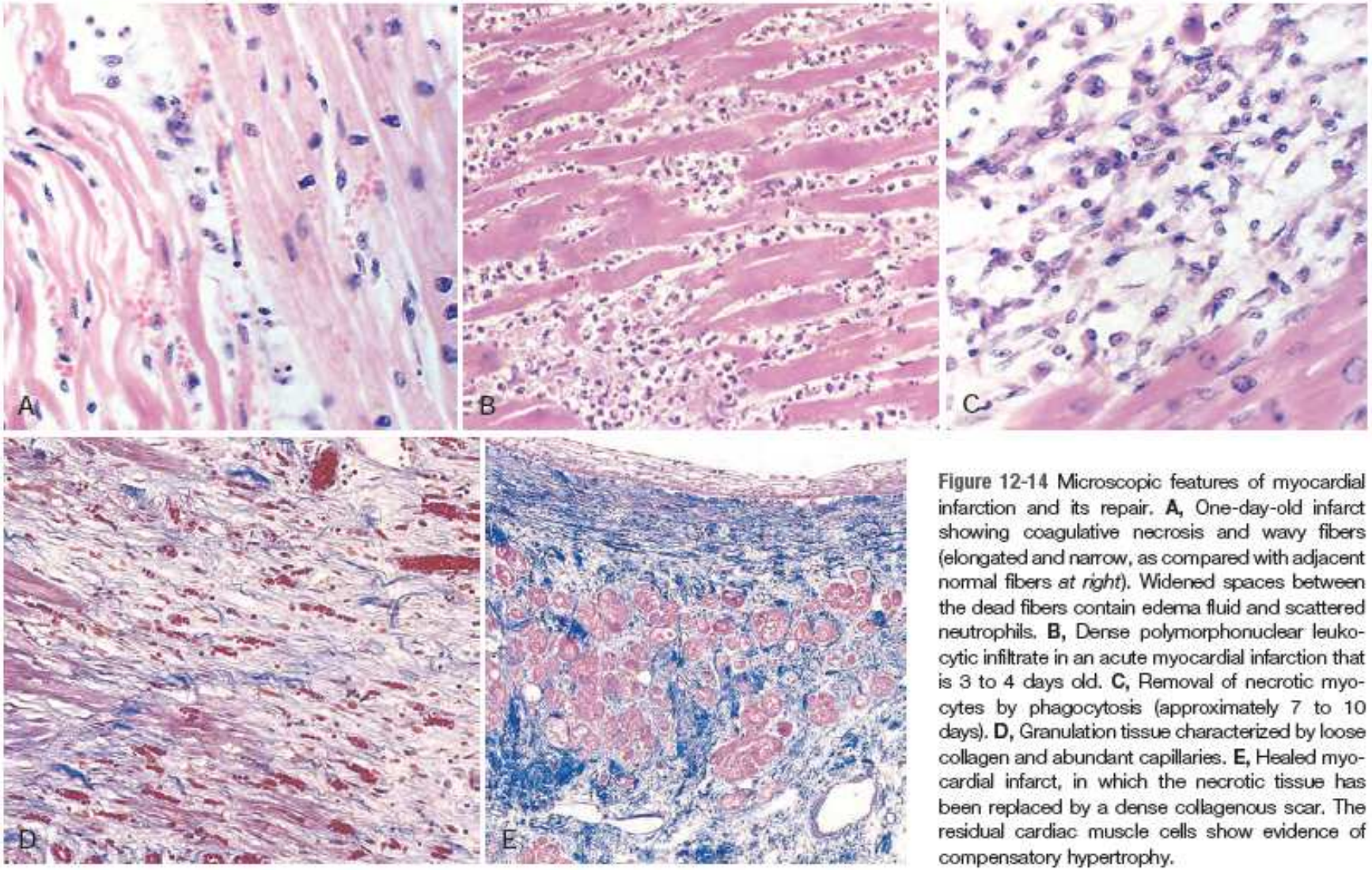


Figure 12-14 Microscopic features of myocardial infarction and its repair. **A,** One-day-old infarct showing coagulative necrosis and wavy fibers (elongated and narrow, as compared with adjacent normal fibers *at right*). Widened spaces between the dead fibers contain edema fluid and scattered neutrophils. **B,** Dense polymorphonuclear leukocytic infiltrate in an acute myocardial infarction that is 3 to 4 days old. **C,** Removal of necrotic myocytes by phagocytosis (approximately 7 to 10 days). **D,** Granulation tissue characterized by loose collagen and abundant capillaries. **E,** Healed myocardial infarct, in which the necrotic tissue has been replaced by a dense collagenous scar. The residual cardiac muscle cells show evidence of compensatory hypertrophy.

Schoen, F and Mitchell, RN, "The Heart," in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

Reperfusion

- Reperfused infarcts are usually hemorrhagic because the vasculature is injured during ischemia and there is bleeding after flow is restored.
- Microscopic examination
- Irreversibly injured myocytes exhibit contraction bands
- Intensely eosinophilic intracellular “stripes” composed of closely packed sarcomeres.
- Result from the exaggerated contraction of sarcomeres when perfusion is reestablished as are exposed to a high concentration of Ca^{2+}

Reperfusion

- Reperfusion not only salvages reversibly injured cells but also alters the morphology of lethally injured cells.
- Reperfusion injury.
- Leads to arrhythmias, hemorrhage.

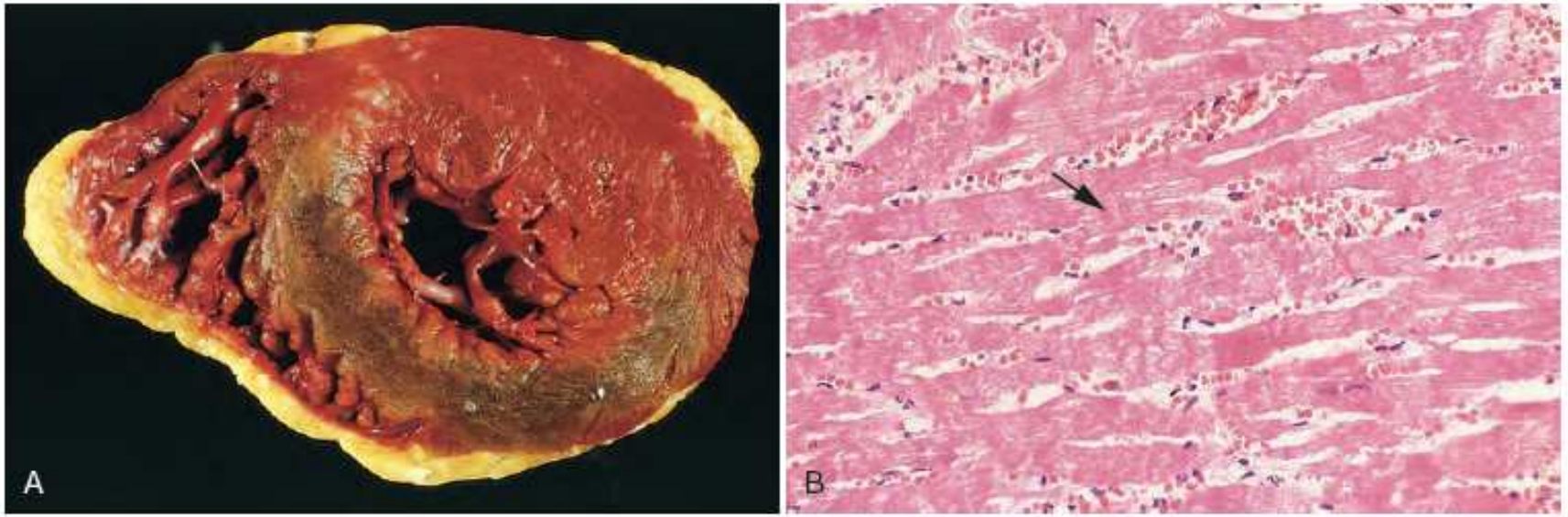


Figure 12-15 Consequences of myocardial ischemia followed by reperfusion. Gross **(A)** and microscopic **(B)** appearance of myocardium modified by reperfusion. **A,** Large, densely hemorrhagic, anterior wall acute myocardial infarction in a patient with left anterior descending artery thrombus treated with streptokinase, a fibrinolytic agent (triphenyl tetrazolium chloride-stained heart slice). Specimen oriented with posterior wall at top. **B,** Myocardial necrosis with hemorrhage and contraction bands, visible as dark bands spanning some myofibers *(arrow)*.

Schoen, F and Mitchell, RN, "The Heart," in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

Structural complications of myocardial infarction

- Free wall rupture leads to a hemopericardium, which causes cardiac tamponade.
- Interventricular septum rupture leads to a left-to-right shunt;
- Papillary muscle rupture (or simply death of the papillary muscle) leads to acute mitral insufficiency.
- Women, <60 years of age, preexisting hypertension, and no prior infarcts (fibrosis of the myocardium caused by a prior infarct protects against rupture) are the major risk factors for rupture.
- An aneurysm may result as the weakened scarred wall bulges outward with each contraction.

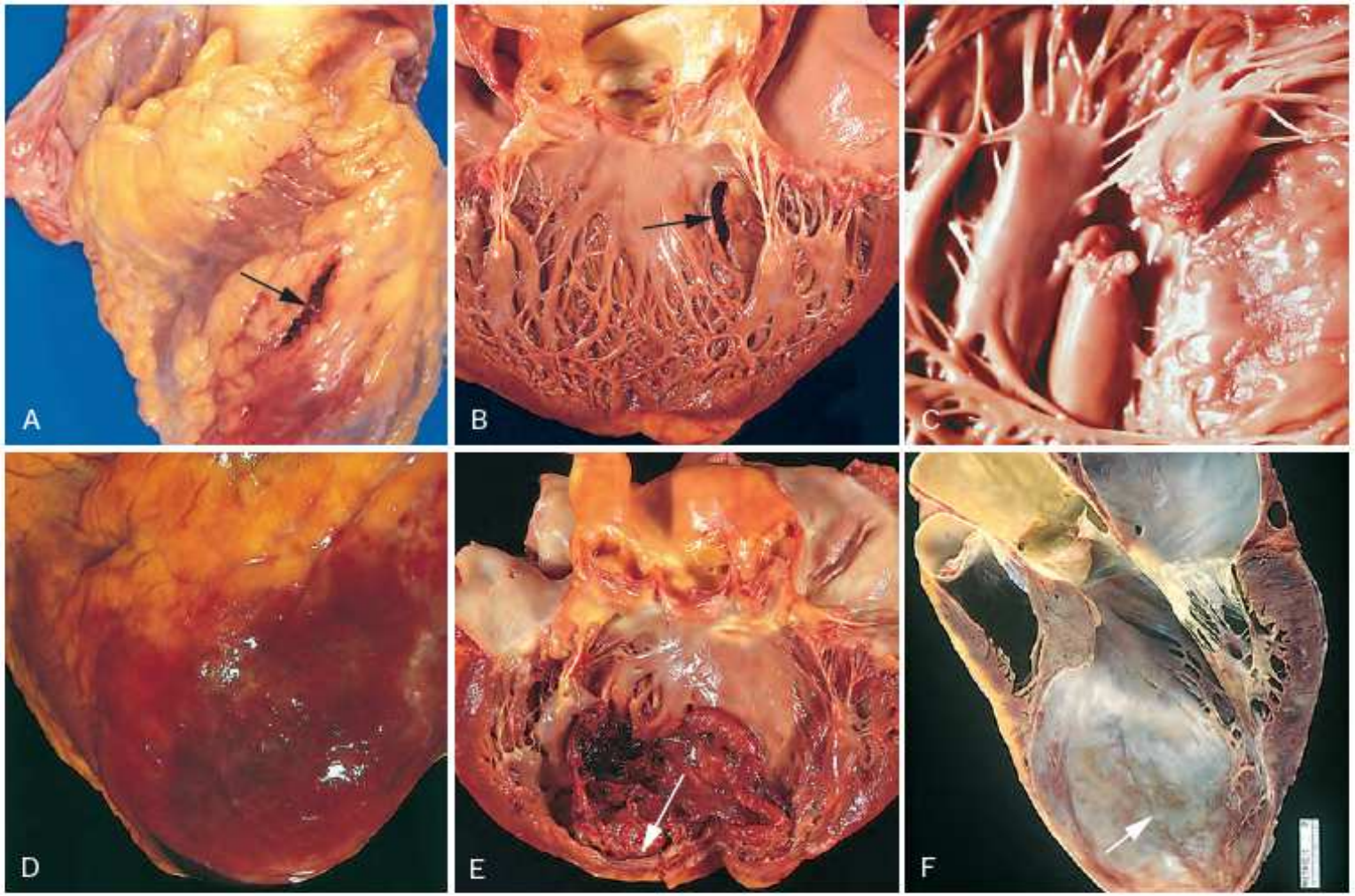


Figure 12-18 Complications of myocardial infarction. **A,** Anterior myocardial rupture in an acute infarct *(arrow)*. **B,** Rupture of the ventricular septum *(arrow)*. **C,** Complete rupture of a necrotic papillary muscle. **D,** Fibrinous pericarditis, showing a dark, roughened epicardial surface overlying an acute infarct. **E,** Early expansion of anteroapical infarct with wall thinning *(arrow)* and mural thrombus. **F,** Large apical left ventricular aneurysm. The left ventricle is on the right in this apical four-chamber view of the heart. (**A-E,** Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989; **F,** Courtesy William D. Edwards, MD, Mayo Clinic, Rochester, Minn.)

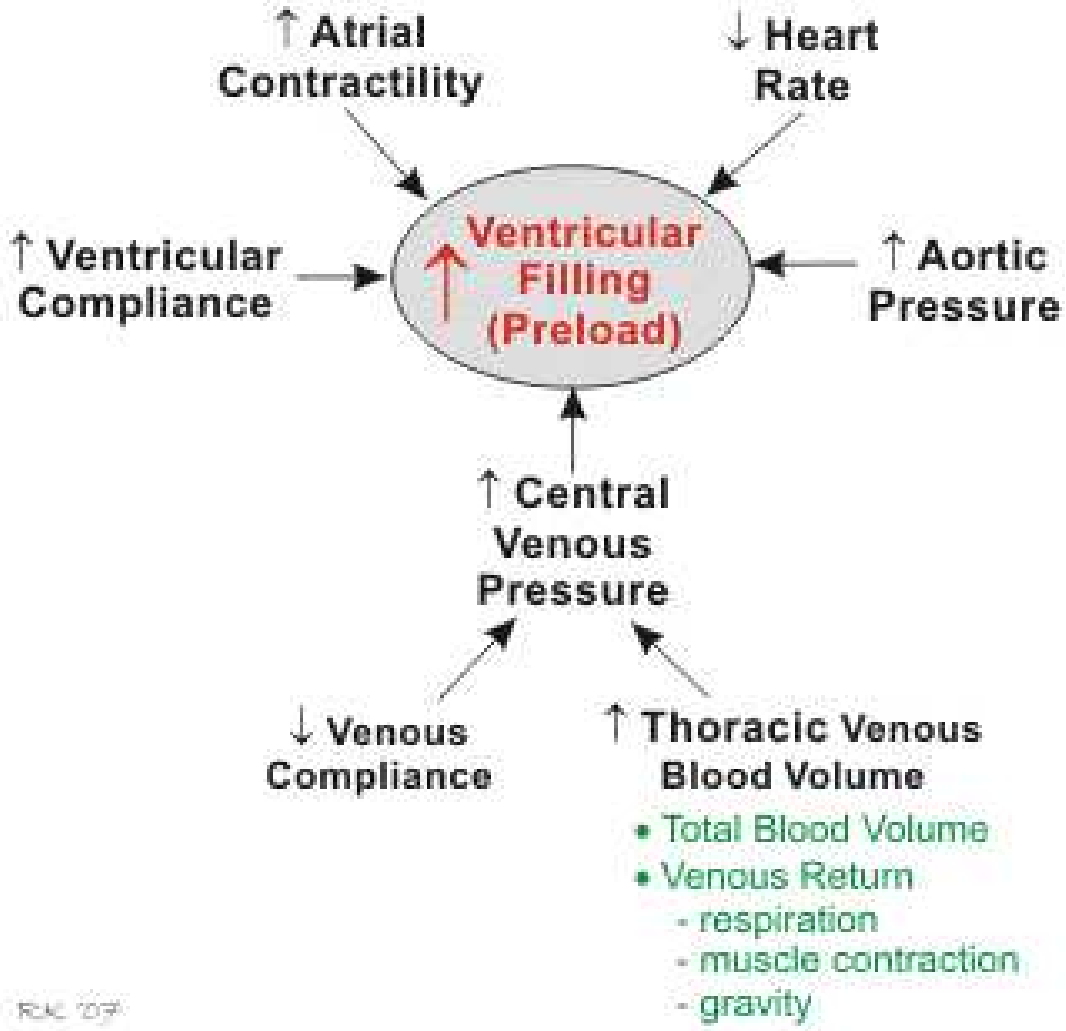
Schoen, F and Mitchell, RN, “The Heart,” in Kumar, V, Abbas, AK, Aster, JC (eds), Robbins and Cotran The Pathologic Basis of Disease (9th ed.), 2015. Elsevier. Philadelphia.

Congestive heart failure

- Dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea are signs of left ventricular failure
- May be present with isolated diastolic heart failure (CHF with preserved ejection fraction) as well as with diastolic and systolic dysfunction (CHF)
- Peripheral edema reflects right ventricular failure

Preload

- The initial stretching of the cardiac myocytes prior to contraction
- Related to muscle sarcomere length.
- When venous return to the heart is increased, the end-diastolic pressure and volume of the ventricles are increased, which stretches the sarcomeres, thereby increasing their preload.
- Increasing preload increases the active tension developed by the muscle fiber and increases the velocity of fiber shortening at a given afterload and inotropic state.



https://www.cvphysiology.com/Cardiac%20Function/CF007

Afterload

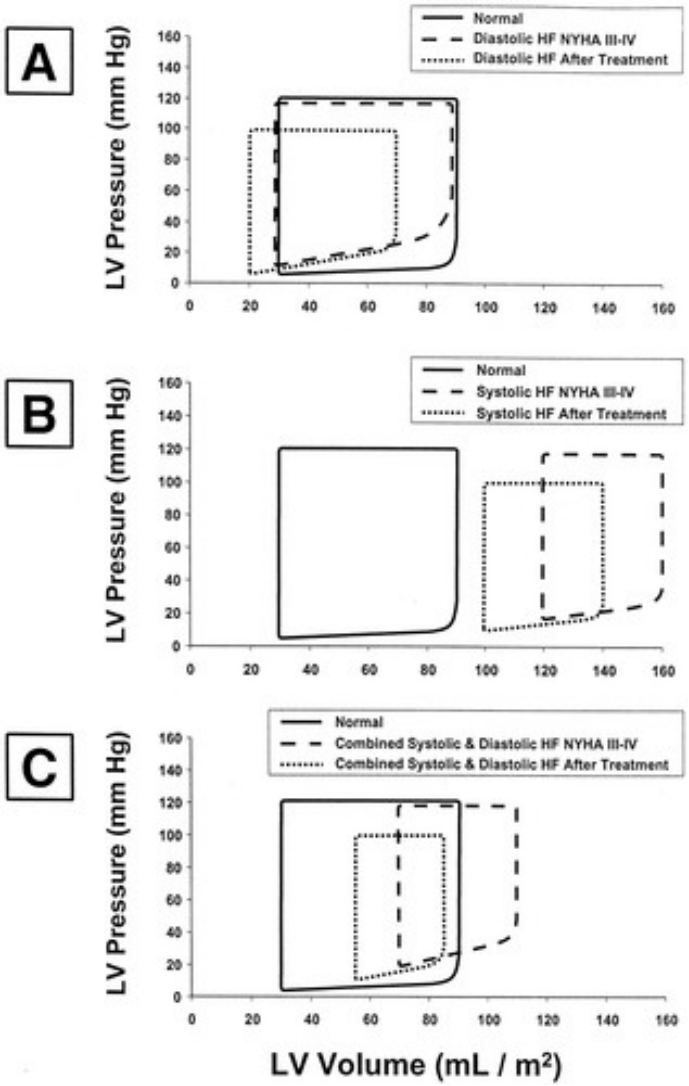
- The tension or stress in the ventricular wall immediately prior to ejection.
- This resistance to outflow of the left ventricle is closely related to the aortic pressure.
- Afterload is often expressed as ventricular wall stress:
- $Pr/2h = \sigma$ (but is geometry dependent)
- Resistance of the vascular system = ΔP across the arterial circuit / cardiac output or mean flow = 8μ (viscosity of blood) Length of the arterials system $/\pi r^4$
- Wall stress is wall tension divided by wall thickness

Afterload

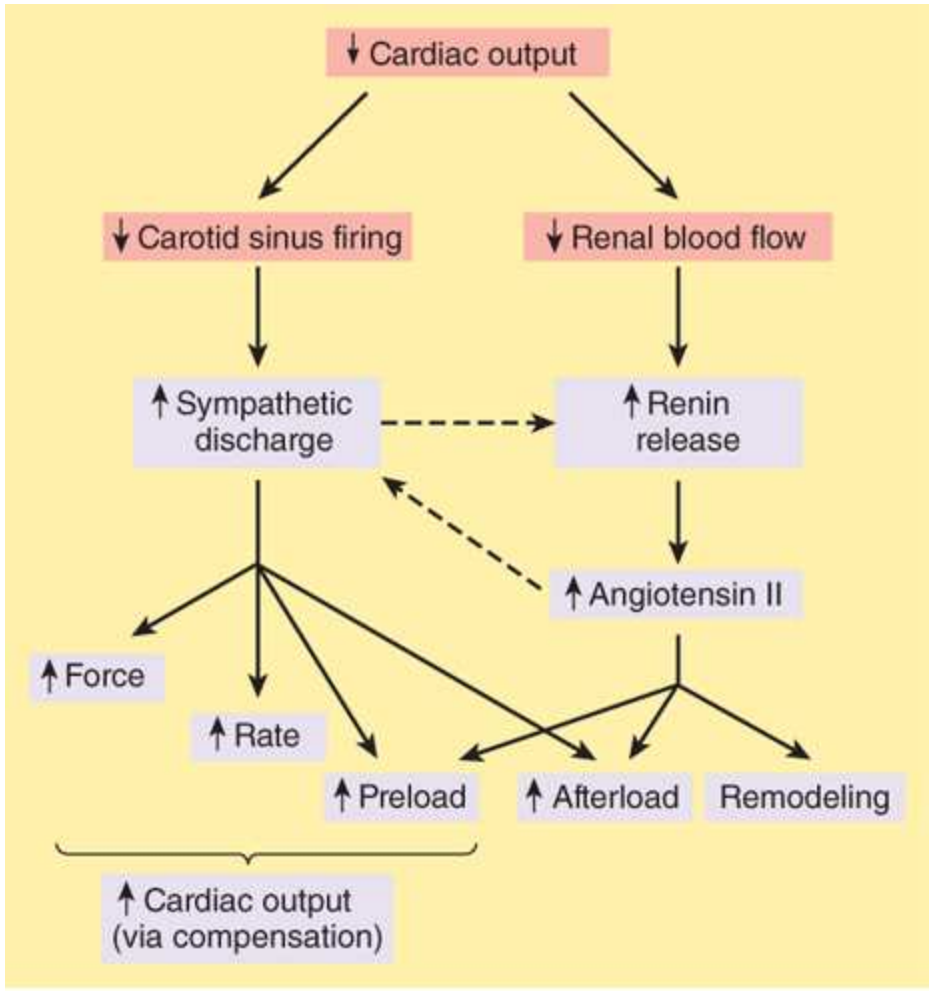
- Wall stress and therefore afterload are increased by an increase in ventricular inside radius (ventricular dilation).
- Lower SV and higher LVEDP
- A hypertrophied ventricle, which has a thickened wall, has less wall stress and reduced afterload.
- Higher SV and lower LVEDP

Diastolic and systolic dysfunction

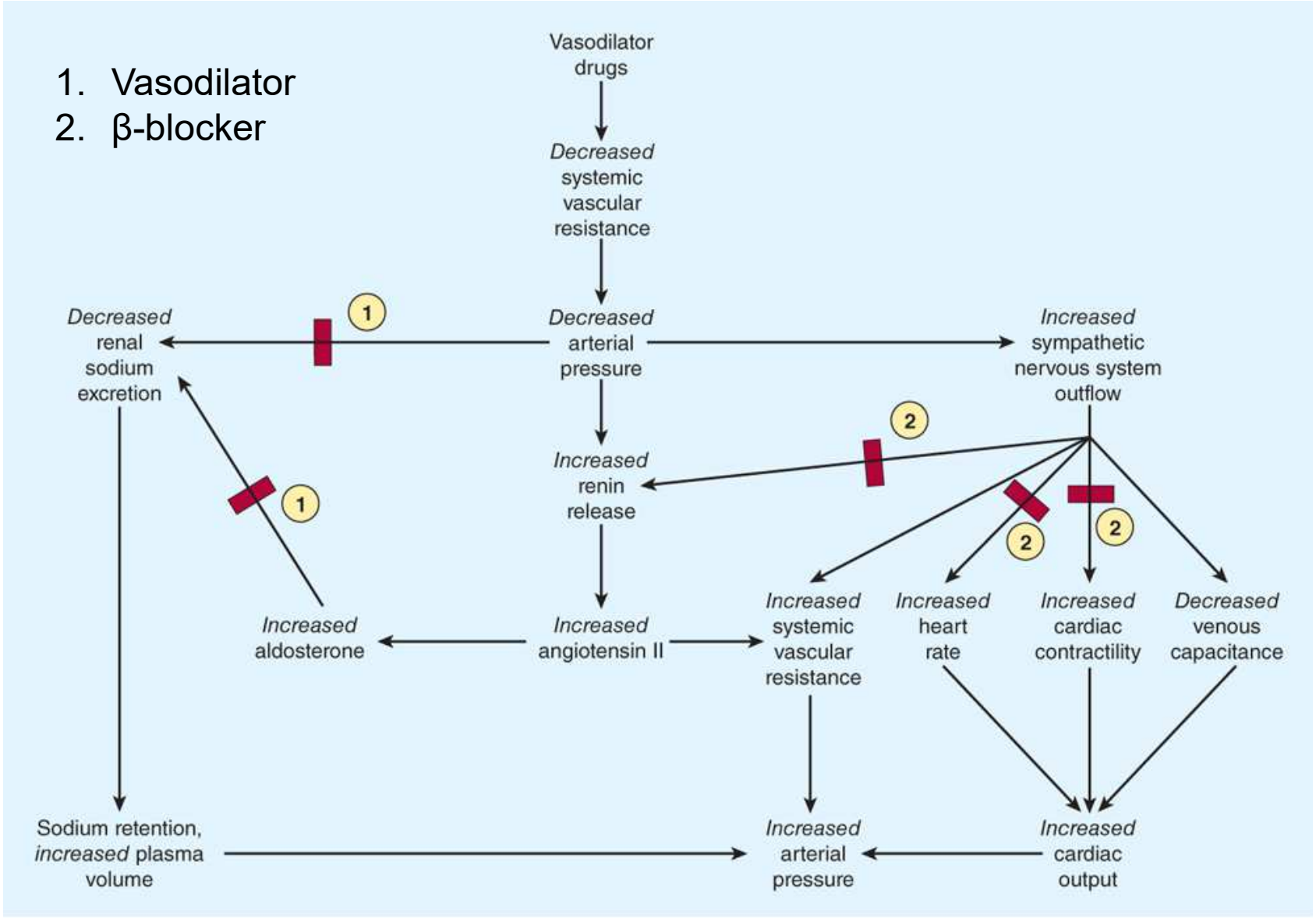
- Systolic dysfunction
- Ejection fraction (EF) is not preserved
- Decrease in stroke volume
- Diastolic dysfunction
- Increase in end-diastolic volume, and a marked increase in end-diastolic pressure
- Decreased LV compliance.
- Myocardium loses its ability to generate force and shorten and return to an unstressed length and force

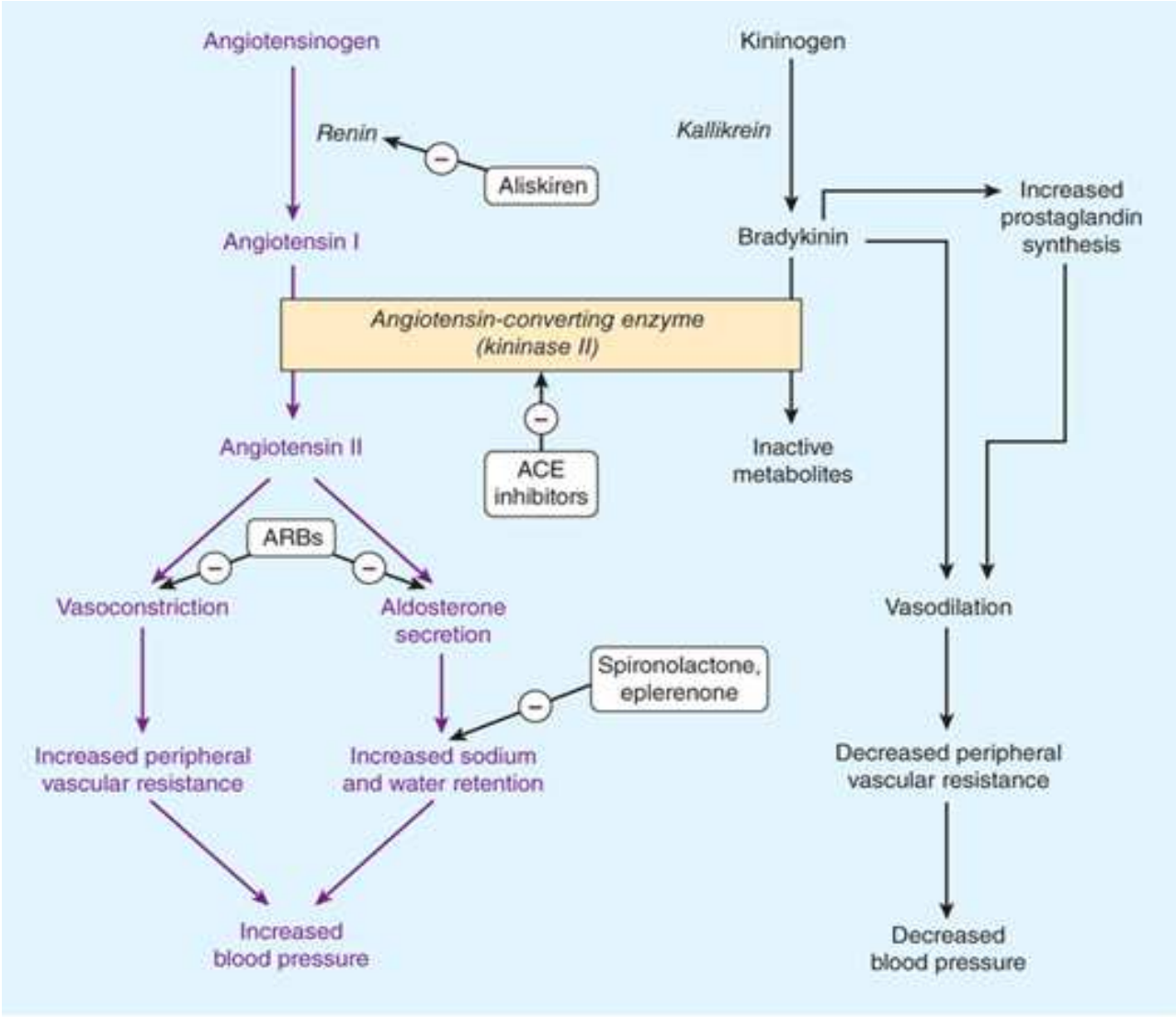


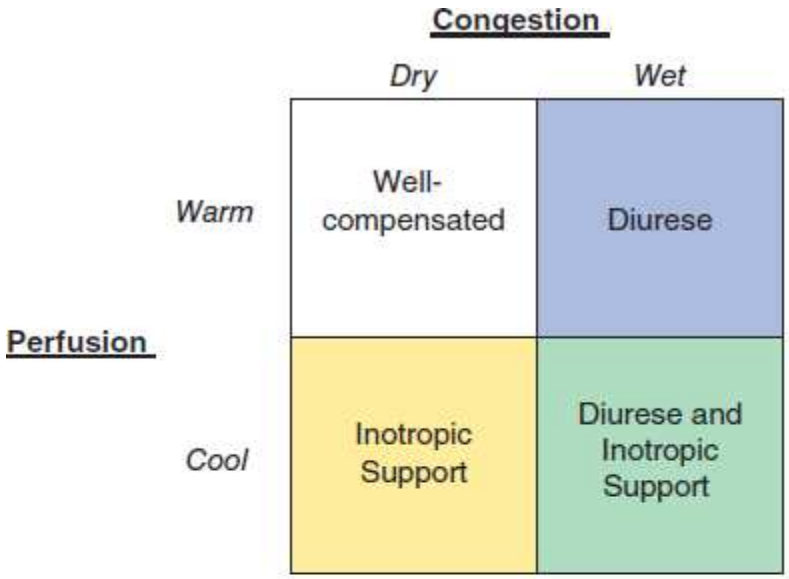
Michael R. Zile. Circulation. New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part I, Volume: 105, Issue: 11, Pages: 1387-1393, DOI: (10.1161/hc1102.105289)



1. Vasodilator
2. β-blocker







Signs/Symptoms of Low Perfusion

- Narrow pulse pressure
- Cool extremities
- Altered mental status
- Decreased urine output

Signs/Symptoms of Congestion

- Orthopnea/paroxysmal nocturnal dyspnea
- Edema/ascites
- Elevated JVP
- Audible S3
- Crackles on lung auscultation
- Hepatojugular reflux
- Valsalva square wave

Source: Navin Kumar, Anica Law: Teaching Rounds: A Visual Aid to Teaching Internal Medicine Pearls on the Wards
www.accessmedicine.com

Table 4 – Comparison between the patients' characteristics in relation to BNP values ≥ 1,400 and <1,400 pg/dL

	BNP		
Characteristics	≥1,400 pg/dL (n = 78)	<1,400 pg/dL (n = 110)	p
Age (years)	58.7 ± 15.0	58.9 ± 14.0	0.901
Male gender - n (%)	44 (56.4)	65 (59.1)	0.714
Cause of HF - n (%):			
Chagasic	29 (37.2)	20 (18.2)	0.003
Ischemic	15 (19.2)	34 (30.9)	0.072
Non-ischemic (non-chagasic)	34 (43.6)	56 (50.9)	0.322
Vasoactive drugs - n (%)	57 (73.1)	57 (51.8)	0.005
LVEF (%)	23.5 ± 6.6	28.3 ± 10.8	0.002
Baseline urea (mg/dL)	92.0 ± 45.4	74.5 ± 40.6	0.002
Baseline creatinine (mg/dL)	1.7 ± 0.7	1.6 ± 0.7	0.102
BNP (pg/dL)	2,734.0 ± 995.4	781.5 ± 341.8	<0.001
In-hospital death	17 (21.8)	12 (10.9)	0.042
1-year death	40 (51.3)	36 (32.7)	0.011

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

BNP levels also reflect 30 and 180 day mortality post surgery

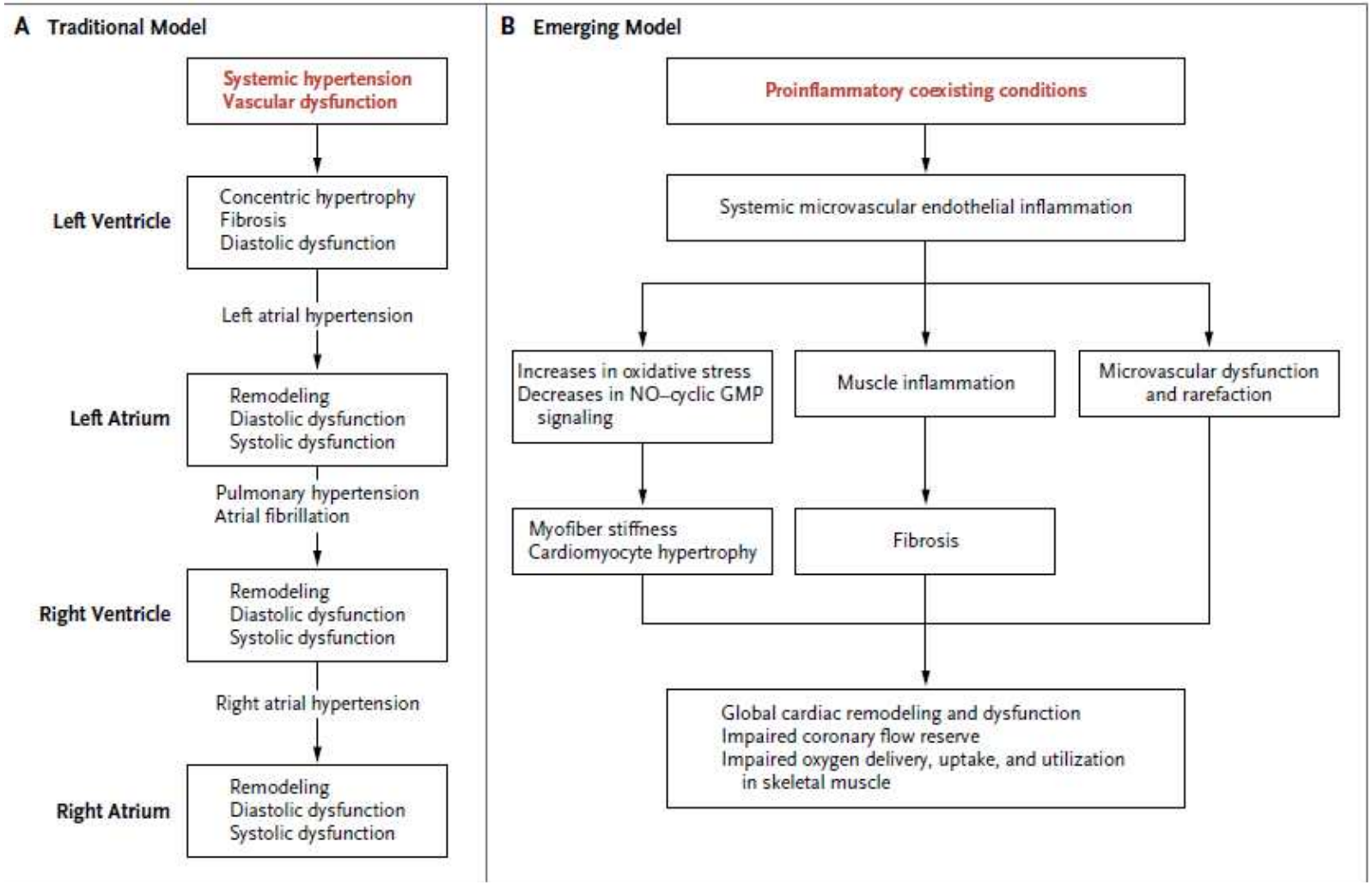
http://www.scielo.br/img/revistas/abc/v100n3/en_a11tab04.jpg
Accessed 01/10/2020

Isolated diastolic heart failure

- Congestive heart failure with preserved ejection fraction
- New model
- Pro-inflammatory coexisting conditions lead to:
- Microvascular endothelial inflammation
- Global cardiac and skeletal-muscle inflammation
- And subsequent fibrosis
- Also lead to increases in oxidative stress that limit nitric oxide–cyclic guanosine monophosphate (NO–cyclic GMP)–protein kinase G signaling
- Promoting global cardiomyocyte hypertrophy and intrinsic myofiber stiffness.

Diastolic dysfunction

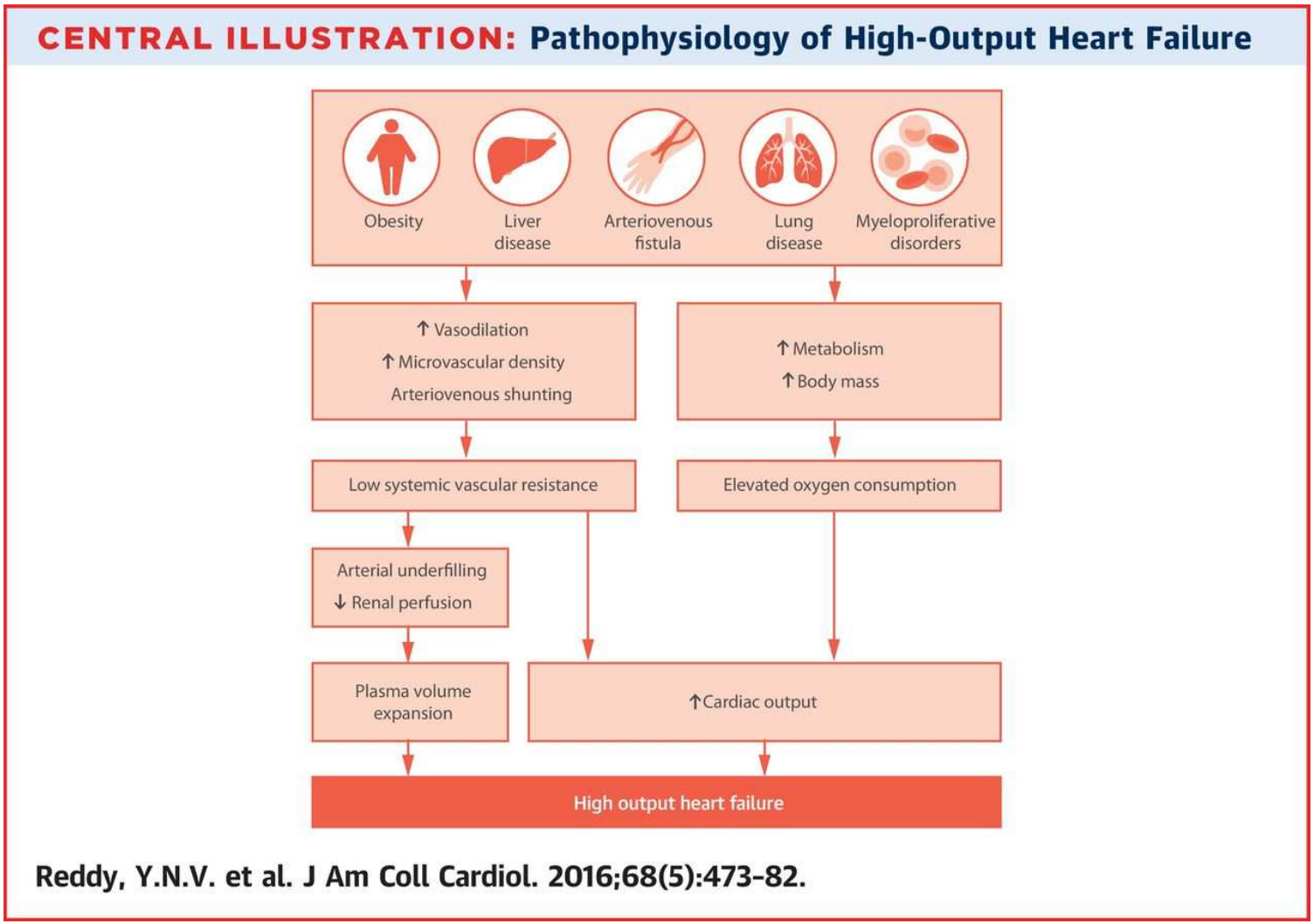
- Finally, coronary microvascular inflammation results in microvascular dysfunction and rarefaction
- Reduced microvascular density and coronary flow reserve.
- Similar changes occur in the skeletal-muscle vasculature with reduced oxygen delivery and utilization.
- Does not respond to usual medications for congestive heart failure with diminished ejection fraction but has better prognosis



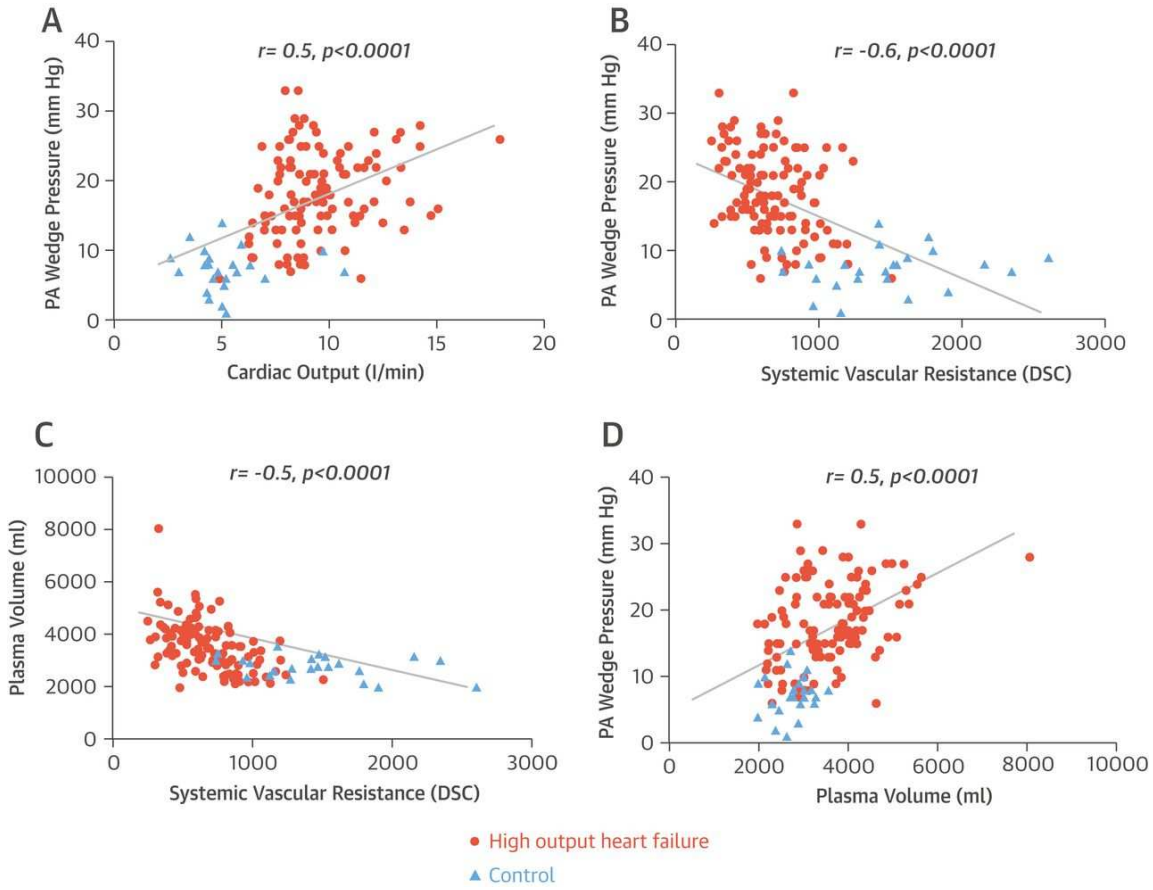
NEJM.org Cases in Primary Care (2017)
Accessed 12/10/2019

High output cardiac failure

- Tachycardia, hypotension, flushing.
- The presence of an increased echocardiographic Doppler-derived cardiac index >3.5 l/min/m^2 should prompt clinicians to consider further evaluation to clarify the diagnosis.
- Resembles congestive heart failure with preserved ejection fraction.



Reddy, YNV, Melenovsky, V, Redfield, MM, Nishimura, RA, Borlaug, BA, "High-Output Heart Failure A 15-Year Experience," Journal of the American College of Cardiology (2016); 68: DOI: 10.1016/j.jacc.2016.05.043 Fig. 1
Accessed 03/10/2020



Reddy, YNV, Melenovsky, V, Redfield, MM, Nishimura, RA, Borlaug, BA, "High-Output Heart Failure A 15-Year Experience," Journal of the American College of Cardiology (2016); 68: DOI: 10.1016/j.jacc.2016.05.043 Fig. 2
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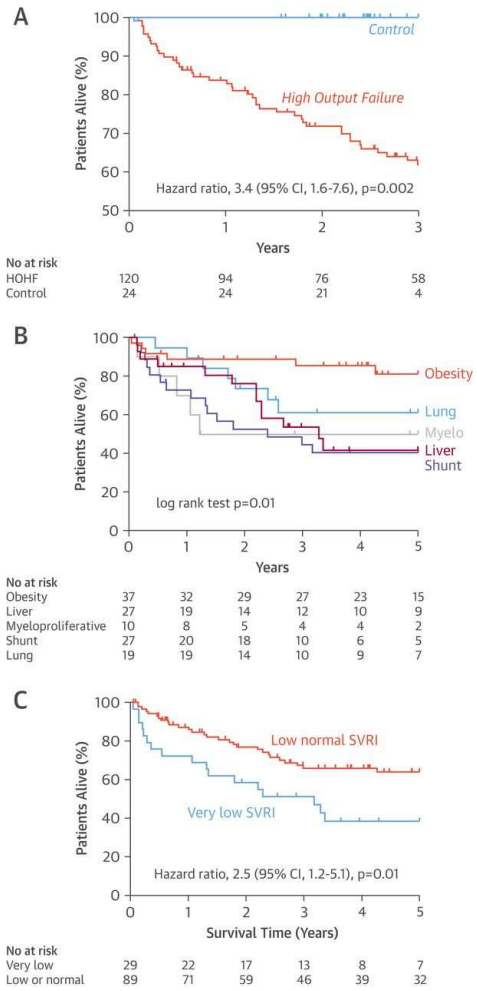


Reddy, YNV, Melenovsky, V, Redfield, MM, Nishimura, RA, Borlaug, BA, "High-Output Heart Failure A 15-Year Experience," Journal of the American College of Cardiology (2016);68: DOI: 10.1016/j.jacc.2016.05.043 Fig. 3
Accessed 03/10/2020

Mechanisms

- Cardiac output increases with:
- Isolated reductions in vascular resistance (cardiac load)
- Oxygen consumption (cardiac demand)
- Excessive systemic vasodilation
- Resting oxygen consumption is increased in high-output heart failure, contributing to the high-output state
- Renal hypoperfusion caused by low vascular resistance promotes sodium retention and increase cardiac work

Mechanisms

- Hypoxia and hypercapnia are associated with:
- High output
- Reduced arterial resistance
- Salt and water retention
- Impaired renal blood flow

TABLE 267-1

Cardiovascular Disease Classification Chart

Class	New York Heart Association Functional Classification
I	Patients have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Canadian Cardiovascular Society Functional Classification
Ordinary physical activity, such as walking and climbing stairs, *does not cause angina*. Angina present with strenuous or rapid or prolonged exertion at work or recreation.
Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions.
Inability to carry on any physical activity without discomfort—anginal syndrome *may* be present at rest.

AAC/AHA stage classification

- Stage A: High risk of heart failure, without structural heart disease or symptoms
- Stage B: Heart disease with asymptomatic left ventricular dysfunction
- Stage C: Prior or current symptoms of heart failure
- Stage D: Refractory end stage heart failure

Congestive heart failure treatment summary

- DASH diet
- SGLT2 inhibitor if diabetic
- Avoid thiazolidendiones
- If pro-BNP>300 pg/ml at any age, even if asymptomatic, therapeutic intervention indicated
- Loop diuretics
- Mineralicorticoid inhibitors
- Angiotensin receptor blocker with neprisylin is now the preferred therapy

Congestive heart failure treatment summary

- Carvedilol is added to all patients post-myocardial infarction with diminished LVEF
- Avoid diliatizem, verapamil as they depress myocardial function
- CoQ_{10} , Omega-3, Polyunsaturated fatty acid supplementation may be beneficial
- Hydralazine with oral nitrates beneficial in those of African heritage

Diuretics

Class	Mechanism of action	Adverse effects
Thiazide	Inhibits Na^+ /Cl^- symporter in distal tubule, leading to diminished reabsorption of Na^+; Ca^{2+} reabsorption increases	Uric acid excretion impaired; worsen lipid profile, hyperglycemia; hypokalemia;
Loop Furosemide, Butamide	Inhibits Na^+-K^+-Cl^- channel in ascending limb of loop of Henle (block reabsorption); increase Ca^{2+} loss as lumen positive potential falls	Uric acid excretion impaired; hypokalemia; ototoxic
Potassium Sparing Triamterene Mineralicorticoid Inhibitor Spironolactone	Inhibit Na^+ transport in distal tubule and collecting duct Aldosterone antagonist	Hyperkalemia
Carbonic Anhydrase Inhibitor	Inhibit conversion of bicarbonate to CO_2 in proximal convoluted tubule	Metabolic acidosis; paresthesias
Osmotic	Enhance water excretion	

Anti-hypertensive agents

Agent	Mechanism	Adverse effects
Methyldopa Clonidine	Centrally acting α_2 agonists	Positive Coomb's test Rebound hypertension
Prazosin, doxazosin, terazosin, phentolamine	α-blockers	Relax bladder sphincter (treat urinary hesitancy)
Propanolol Atenolol, metoprolol, esmolol Carvedilol	Non selective β-blockers β_1-blockers Mixed α and β blockers	Bradycardia may be noted with all β-blockers Bronchoconstriction is not seen with selective blockers Decreased systemic vascular resistance is noted with all; cardiac output also falls
Nifedipine, amlodipine	Vasoselective L-type Calcium channel blockers	Constipation, bradycardia
Diltiazem	Nonselective L-type Calcium channel blocker	Diminished cardiac contractility

Anti-hypertensive agents

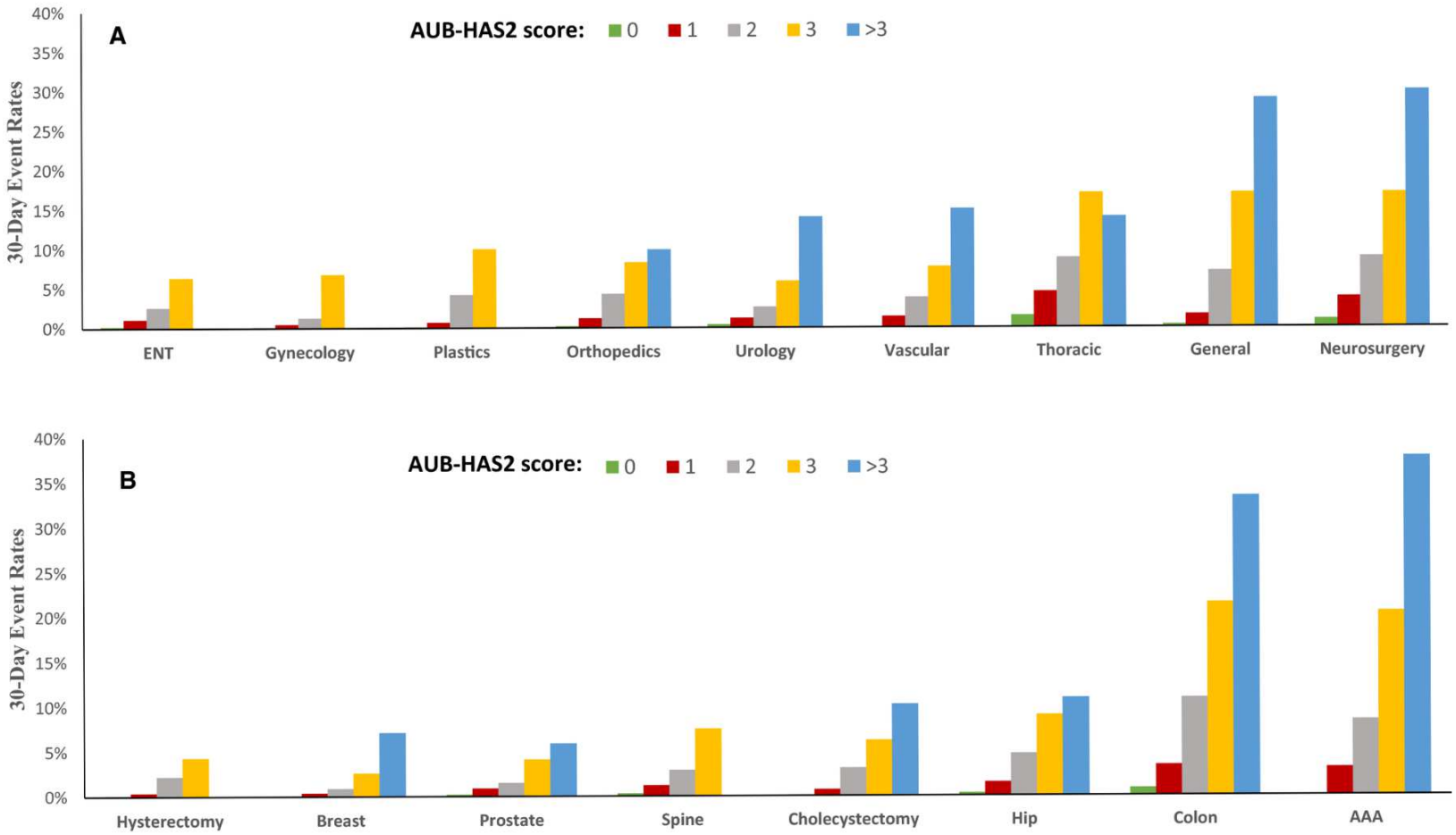
Agent	Mechanism	Adverse effects
Nitroprusside	Nitrous oxide release	Cyanide generation
Nitroglycerin	Nitrous oxide release	
Hydralazine	Opens K+ channels	Drug induced SLE
Minoxidil		Hirsutism, Sodium retention
Captopril, lisinopril, enalapril	Angiotensin converting enzyme and bradykinin inhibitors	Cough, hyperkalemia, proteinuria, angioedema, fetal renal defects
Losartan, valsartan	Angiotensin II receptor blockers	Cough, hyperkalemia, proteinuria, angioedema, fetal renal defects
Neprisylin inhbitor	Endopeptidase inhibitor	
Fenoldopam	Peripheral D1-receptor blocker	

Table 1. Elements of the AUB-HAS2 and Revised Cardiac Risk Indices

AUB-HAS2 Cardiovascular Risk Index	Revised Cardiac Risk Index
• History of heart disease • Symptoms of heart disease (angina or dyspnea) • Age ≥75 years • Anemia (hemoglobin <12 mg/dL) • Vascular surgery • Emergency surgery	• History of ischemic heart disease • History of congestive heart failure • History of cerebrovascular disease • Diabetes mellitus on insulin • Creatinine >2 mg/dL • High-risk surgery

AUB indicates The American University of Beirut.

Habib A. Dakik. Journal of the American Heart Association. AUB-HAS2 Cardiovascular Risk Index: Performance in Surgical Subpopulations and Comparison to the Revised Cardiac Risk Index, Volume: 9, Issue: 10, DOI: (10.1161/JAHA.119.016228



Habib A. Dakik. Journal of the American Heart Association. AUB-HAS2 Cardiovascular Risk Index: Performance in Surgical Subpopulations and Comparison to the Revised Cardiac Risk Index, Volume: 9, Issue: 10, DOI: (10.1161/JAHA.119.016228)

Kawasaki disease

- Leading cause of acquired heart disease in children
- At least 5 days of fever and four of five of following:
  - Conjunctival injection without exudate
  - Mucous membrane changes (lips/tongue/pharynx)
  - Peripheral extremity changes (hand/foot erythema and/or swelling)
  - Polymorphous generalized rash
  - Unilateral enlarged cervical lymph node (> 1.5 cm)

Kawasaki disease

- Exclusion of other causes of these findings
- Dilated coronary arteries from echocardiograms can help with diagnosis in incomplete Kawasaki disease (KD)
- 80% present <5 years of age
- Girls 1.5:1

Table 20–14.

Noncardiac manifestations of Kawasaki disease.

System	Associated Signs and Symptoms
Gastrointestinal	Vomiting, diarrhea, gallbladder hydrops, elevated transaminases
Blood	Elevated ESR or CRP, leukocytosis, hypoalbuminemia, mild anemia in acute phase and thrombocytosis in subacute phase (usually second to third week of illness)
Renal	Sterile pyuria, proteinuria
Respiratory	Cough, hoarseness, infiltrate on chest radiograph
Joint	Arthralgia and arthritis
Neurologic	Mononuclear pleocytosis of cerebrospinal fluid, irritability, facial palsy

Kawasaki disease

- Coronary artery lesions range from mild transient dilation of a coronary artery to large aneurysms.
- Aneurysms rarely form before day 10 of illness.
- Untreated patients have a 15%–25% risk of developing coronary aneurysms.
- Those at greatest risk for aneurysm formation are males, young infants (< 6 months), and those not treated with intravenous immunoglobulin (IVIG).

Kawasaki disease

- Most coronary artery aneurysms resolve within 5 years of diagnosis
- 19% of all aneurysms develop associated obstruction or stenosis
- May lead to coronary ischemia
- Giant aneurysms (> 8 mm) are less likely to resolve, and nearly 50% eventually become stenotic.
- Acute thrombosis of an aneurysm can occur, resulting in myocardial infarction that is fatal in approximately 20% of cases.

Treatment

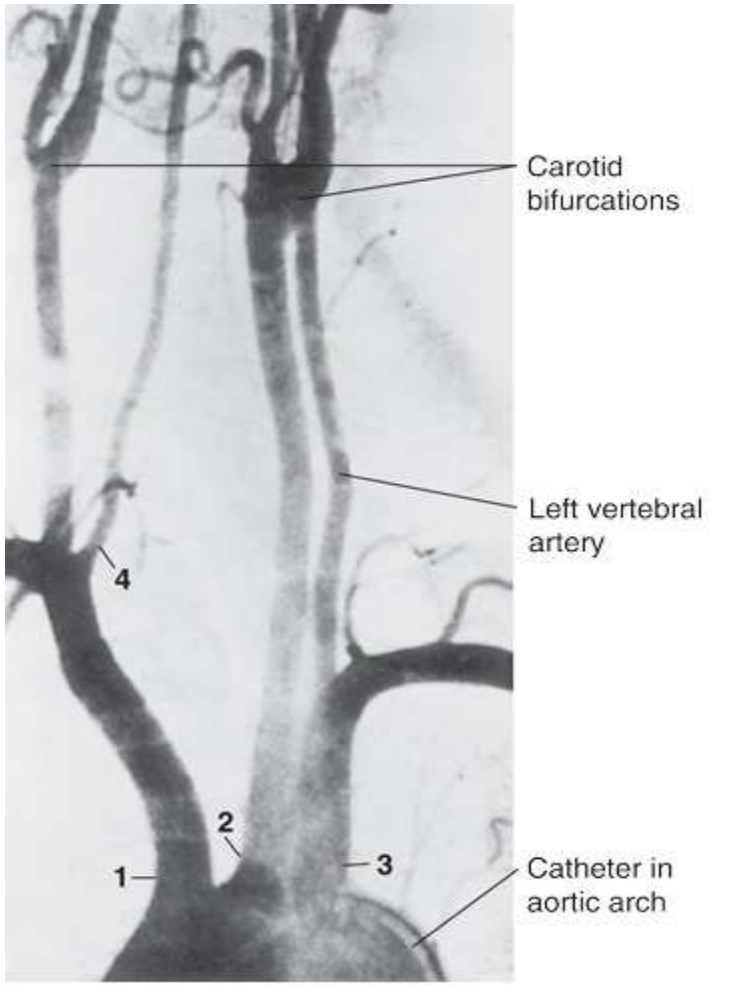
- Intravenous immunoglobulin
- Corticosteroids if fever does not resolve with two doses of immunoglobulin
- ASA

Table 20–15.

Long-term management in Kawasaki disease.

Risk Level	Definition	Management Guidelines
I	No coronary artery changes at any stage of the illness	No ASA is needed beyond the subacute phase (6–8 wk). No follow-up beyond the first year.
II	Coronary dilation only (Z-score[a] 2–2.5)	Same as above or clinical follow-up every 2–5 y if persistent coronary dilation.
III	Small coronary aneurysms (Z-score > 2.5 to < 5)	ASA until abnormality resolves. Assess at 6 mo and every 2–3 y thereafter with ECG and echo if < 7 y and every other-year stress testing if > 7 y.
IV	Medium aneurysms (Z-score > 5 to < 10 and absolute dimension < 8 mm)	Long-term ASA ± clopidogrel. Annual follow-up with ECG, echo, and stress testing.
V	Large and giant aneurysms (Z-score > 10 or absolute dimension > 8 mm) or coronary artery obstruction	Long-term ASA ± clopidogrel ± warfarin ± calcium channel blocker to reduce myocardial oxygen consumption. Echo and ECG every 6 mo. Stress testing and Holter examination annually.

Aortic arch vessels



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

1: Brachiocephalic artery;
2: Common carotid artery;
3: Left subclavian artery;
4: Right vertebral artery.

(Reproduced, with permission, from Peele TL: *The Neuroanatomical Basis for Clinical Neurology.* Blakiston, 1954.)

Fig. 22-2 Accessed 04/01/2010

Carotid artery disease

- The prevalence of carotid artery stenosis varies from 0.5% in those <50 years of age to 10% in those >90 years of age.
- Transient ischemic attack or embolic event.
- A bruit over the vessel has a positive likelihood ratio (LR+) of 4.0 for stenosis >70% in that vessel.
- The absence of a bruit does not exclude carotid artery stenosis.
- Carotid endarterectomy in asymptomatic patients with >70% occlusion or in patients with 50% occlusion and a history of TIA or embolic events.

Subclavian steal syndrome

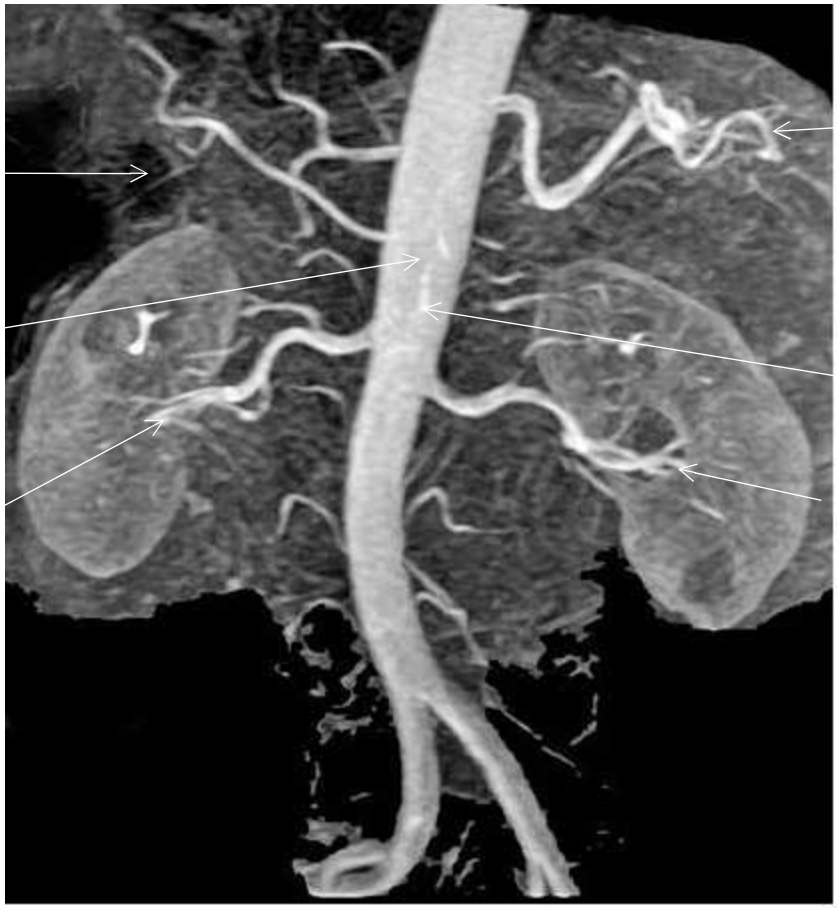
- Ipsilateral arm movement steals blood from vertebral circulation.
- Upper extremity claudication.
- Claudication is exertion induced pain within a muscle group that disappears after 1-5 minutes of rest.
- Vertigo, ataxia, syncope, or blindness.
- Bruit present above clavicles.
- Discrepancy in blood pressure between arms.
- Treated with surgical bypass.

MRI Aortogram

Hepatic artery

Celiac artery origin

Right renal artery



Splenic artery

Superior mesenteric artery origin

Left renal artery

Fig. 23-46 Accessed 04/01/2010

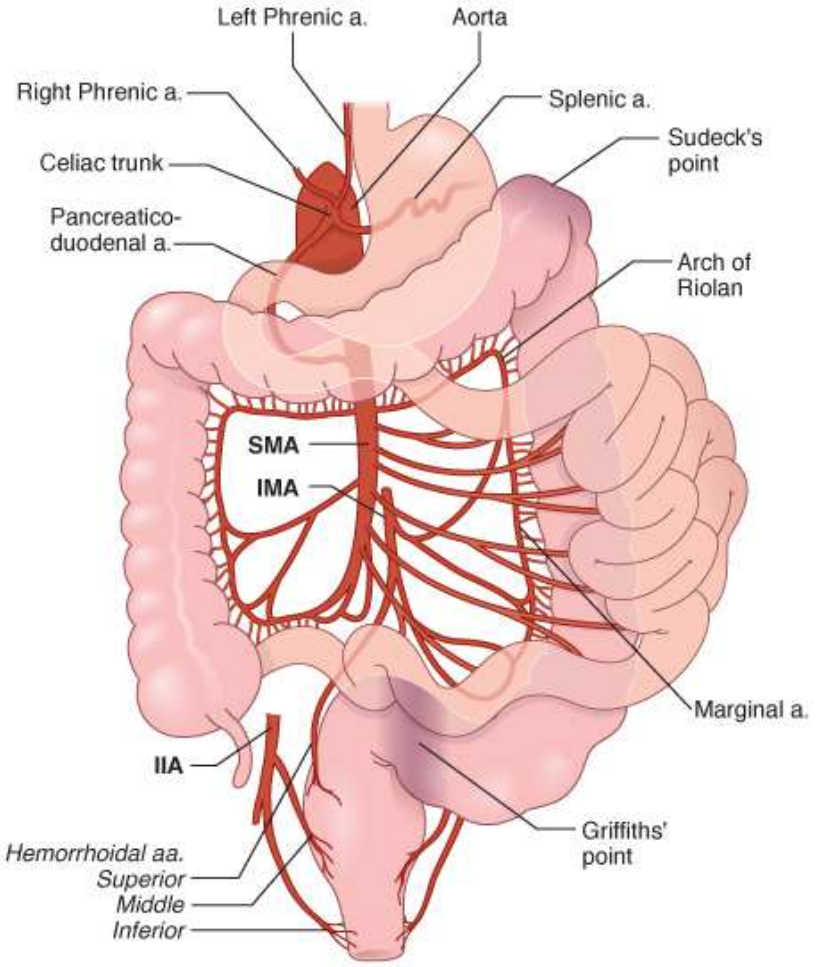
Abdominal bruits

- Prevalence in general population is 1-5%.
- 7-31% of young persons have benign bruits.
- 20% of whites have renovascular hypertension; less likely in blacks
- LR+, 39 for renovascular hypertension if:
- Systolic-diastolic abdominal bruit is found, and is in:
- A hypertensive <30 years of age;
- Or in renal failure in the absence of proteinuria or abnormal urine sediment;
- Or in renal failure precipitated by ACE inhibitor or angiotensin receptor blocker

Arterial vascular disease

- Renal artery stenosis presents with headache, diastolic hypertension, diminished renal function, and flank bruits.
- ACE inhibitors will cause a fall in blood pressure and lead to renal insufficiency.
- Treat with stent placement.
- Mesenteric ischemia is associated with weight loss, postprandial abdominal pain, and abdominal bruit.
- At least two of the three mesenteric arteries will be occluded (arteriogram).
- Requires bypass or endarterectomy.

Blood supply to the intestine



Sudeck's and Griffiths' points, indicated by shaded area, are watershed areas within the colonic blood supply and common locations for ischemia.

Fig. 292-1 Accessed 08/01/2010

Acute mesenteric ischemia

- Abrupt onset of acute severe abdominal pain out of proportion to a relatively benign physical examination.
- Often no prior symptoms. May have nausea and diarrhea (with blood, late).
- Usually due to embolus to superior mesenteric artery or celiac artery.
- 30% are due to low flow states without obstruction;
- 25%, arterial thrombosis (often with a history of chronic mesenteric ischemia);
- 5%, mesenteric venous thrombosis (portal hypertension).

Acute mesenteric ischemia

- Atrial fibrillation, low cardiac output, hypercoagulable states are risk factors.
- May occur following cocaine use and endurance exercise.
- WBC often markedly abnormal.
- Lactate levels may be elevated (but are not diagnostic).
- Angiography indicated.
- Surgical resection of necrotic bowel and revascularization are principal therapeutic interventions.

Ischemic colitis

- Usually due to non-occlusive decrease in colonic perfusion.
- Typically involves the watershed area at the splenic fexure between superior and inferior mesenteric arteries.
- The sigmoid flexure is supplied by both the inferior mesenteric and internal iliac arteries.
- Repair of an abdominal aortic aneurysm comprises that blood flow in 10% of cases
- Abdominal pain usually mild. Tenderness may be present. Rebound tenderness is uncommon.
- Frequently have bloody diarrhea. Profuse bleeding unusual.

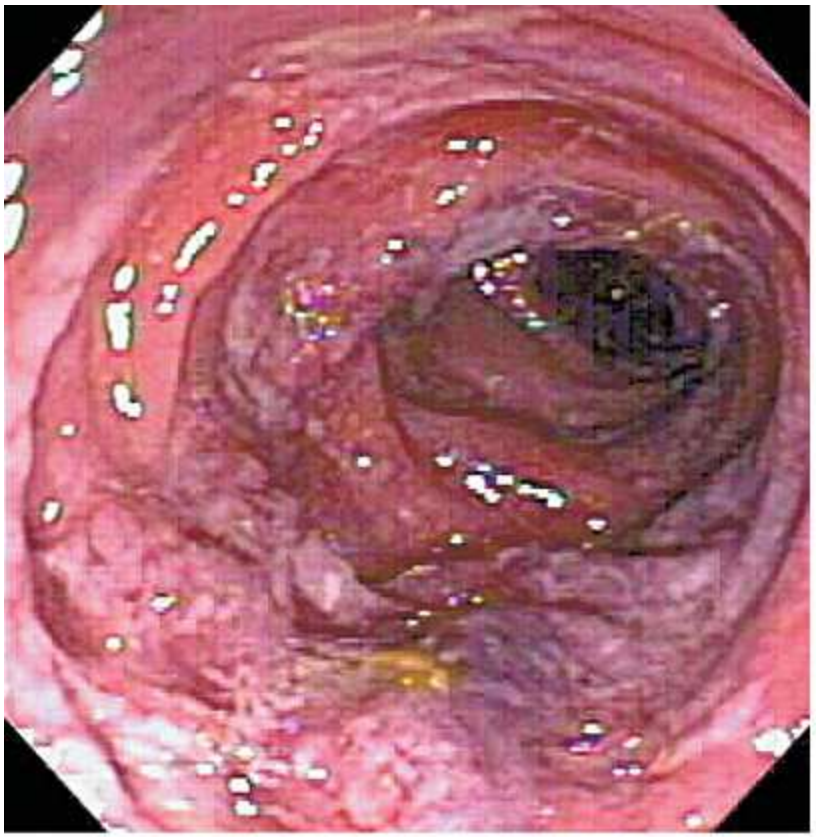
Ischemic colitis

- Hemodialysis, diabetes mellitus, hypoalbuminemia, and use of drugs that induce constipation are associated risk factors.
- Colonoscopy indicated.
- Resting the bowel is often sufficient therapy.

Chronic mesenteric ischemia

- Recurrent postprandial abdominal pain, often diminishing after several hours.
- Obstructive disease of the superior mesenteric artery or celiac artery or both.
- 91% of patients have both vessels involved.
- Weight loss common and is due to food aversion.
- Duplex ultrasonography is very sensitive (>90%). Normal results make the diagnosis unlikely.
- Angiography indicated if diagnosis likely as stenoses alone do not confirm the diagnosis (18% of those over age 65 have stenoses).

Ischemic colitis



D

Ischemic colitis with patchy mucosal edema, subepithelial hemorrhage, and cyanosis.

Fig. e25-4D
Accessed 04/20/10

Aorto-iliac disease

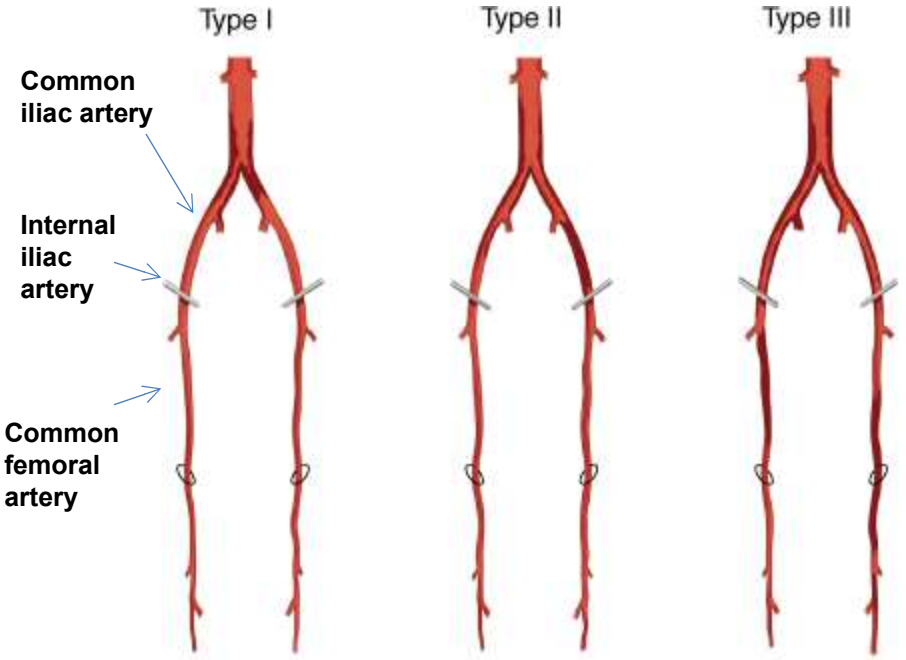


Fig. 23-50 Accessed 04/01/2010

Aortoiliac disease can be classified into three types.

Type I represents focal disease affecting the distal aorta and proximal common iliac artery.

Type II represents diffuse aortoiliac disease above the inguinal ligament.

Type III represents multisegment occlusive disease involving aortoiliac and infrainguinal arterial vessels.

Peripheral arterial disease

- Classically, exertional pain in the calf, relieved by rest. But,
- 47% of patients present with exertional leg pain not in the calf or not relieved by rest
- 42% or patients have no pain at all
- Symptomatic patients will have skin cooler to the touch and the presence of a foot ulcer in the affected leg. (LR+, 5.9)
- The absence of iliac, femoral, and popliteal bruits excludes peripheral arterial disease in a symptomatic patient. (LR-, 0.4)

Peripheral arterial disease

- The presence of a femoral bruit in an asymptomatic patient suggests peripheral arterial disease (LR+ 4.8)
- The presence of an abnormal femoral pulse has an LR+ of 7.2
- The presence of an abnormal posterior tibial pulse has an LR+ of 8.1
- 8% of normal patients do not have a dorsalis pedis pulse
- Capillary refill time adds little to the diagnosis
- Ankle-brachial index of 0.71-0.95 is associated with mild disease; <0.40, severe disease

Peripheral arterial vascular disease

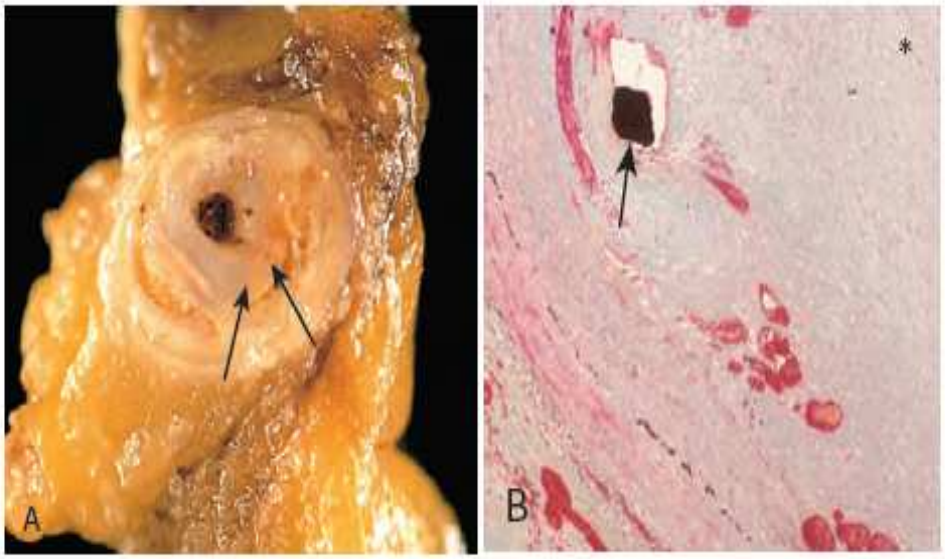
- Most common site of occlusion in the lower extremities is the superficial artery in Hunter's canal.
- Produces calf claudication.
- Arteriogram essential to development of surgical approach.

Leriche syndrome

- Distal aortic occlusion due to atherosclerosis.
- Impotence (hypogastric artery).
- Symmetric lower extremity muscle wasting as well as distal skin thinning and hair loss.
- Claudication of the buttocks.
- Easy fatigability.
- Venous stasis ulcers.
- Absent pulses. (Rest pain is constant and due to hyperperfusion. Worse when supine as gravity assisted blood flow is lost.)
- Requires aortic repair.

Post-intervention changes

Figure 11-34 Restenosis after angioplasty and stenting. **A,** Gross view demonstrating residual yellow atherosclerotic plaque (*arrows*) and a new, tan-white concentric intimal lesion inside of that plaque. **B,** Histologic view shows a thickened neointima separating and overlying the stent wires (the black diamond indicated by the *arrow*), which encroaches on the lumen (indicated by the *asterisk*); Movat stain with matrix staining gray-green. (***B,*** Reproduced from Schoen FJ, Edwards WD. Pathology of cardiovascular interventions, including endovascular therapies, revascularization, vascular replacement, cardiac assist/replacement, arrhythmia control, and repaired congenital heart disease. In Silver MD, Gotlieb AI, Schoen FJ (eds): Cardiovascular Pathology, 3rd ed. Philadelphia, Churchill Livingstone, 2001.)



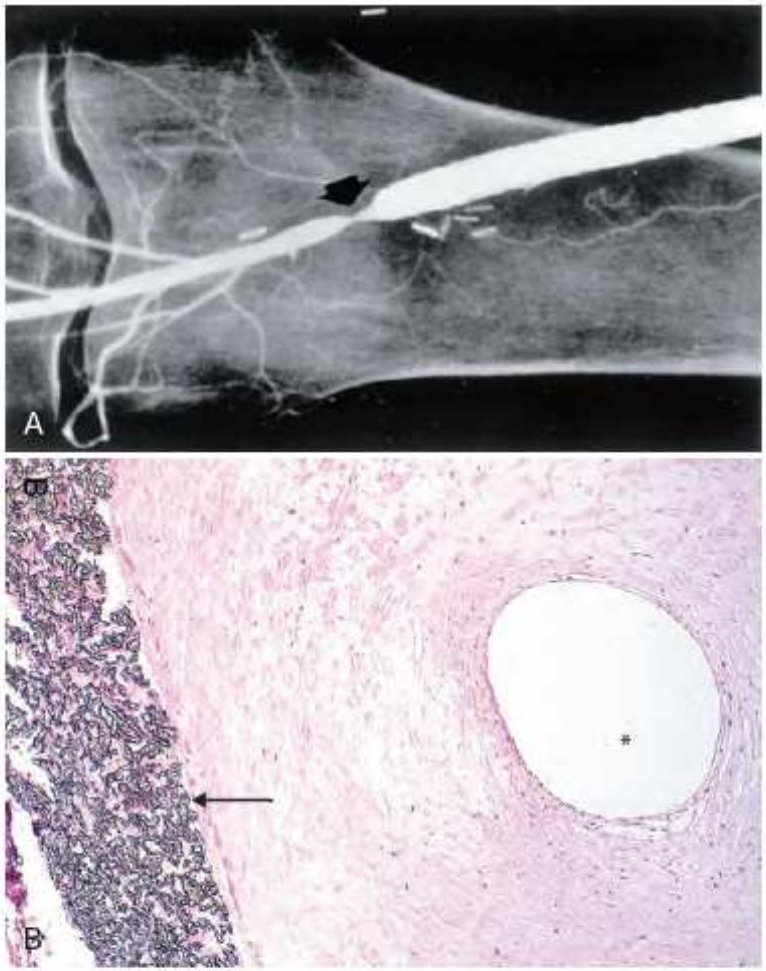


Figure 11-35 Intimal hyperplasia at the distal anastomosis of a synthetic femoral-popliteal graft. **A,** Angiogram demonstrating constriction *(arrow)*. **B,** Photomicrograph demonstrating Gore-Tex graft *(arrow)* with prominent intimal proliferation and very small residual lumen *(asterisk)*. (**A,** Courtesy Anthony D. Whittemore, MD, Brigham and Women's Hospital, Boston, Mass.)

Aneurysm

- To maintain their structural and functional integrity, arterial walls constantly remodel.
- Causes:
- (1) The intrinsic quality of the vascular wall connective tissue is poor.
- Marfan's syndrome
- Defective synthesis of fibrillin
- Abnormal functioning of TGFβ
- Loeys-Dietz syndrome
- Mutations in TGFβ
- Deficient production of elastin as well as collagens type I, III

Aneurysm

- Ehlers-Danlos syndrome
- Abnormal collagen type III
- Vitamin C deficiency (scurvy)
- Collagen cross-linking impaired
- (2) The balance of collagen degradation and synthesis is altered by inflammation and associated proteases
- Elastolytic matrix metalloproteinases (MMPs)
- Diminished expression of tissue inhibitor (TIMPs)

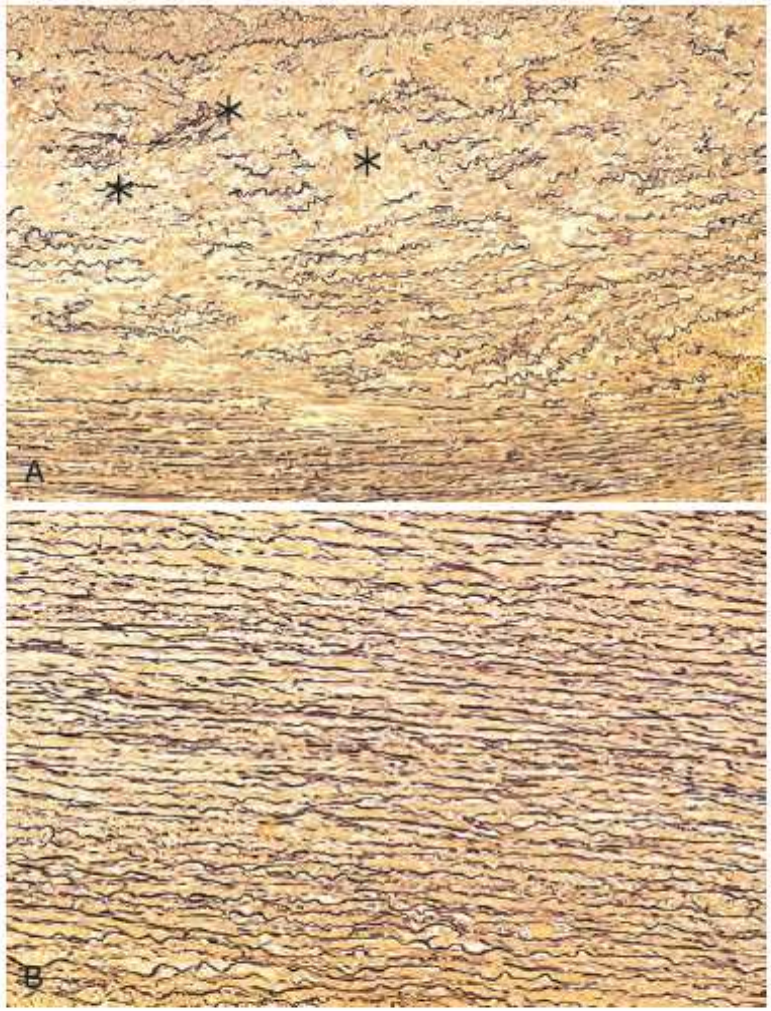


Figure 11-19 Cystic medial degeneration. **A,** Cross-section of aortic media from a patient with Marfan syndrome, showing elastin fragmentation and areas devoid of elastin that resemble cystic spaces but are actually filled with proteoglycans *(asterisks)*. **B,** Normal media for comparison, showing the regular layered pattern of elastic tissue. In both **A** and **B**, elastin is stained black.

Aneurysm

- (3) The vascular wall is weakened through loss of smooth muscle cells or the synthesis of non-collagenous or non-elastic extracellular matrix.
- Systemic hypertension may lead to ischemia of medial vessels (cystic medial degeneration)
- Obliterative endarteritis of small vessels (characteristic of tertiary syphilis)
- Fibromuscular dysplasia

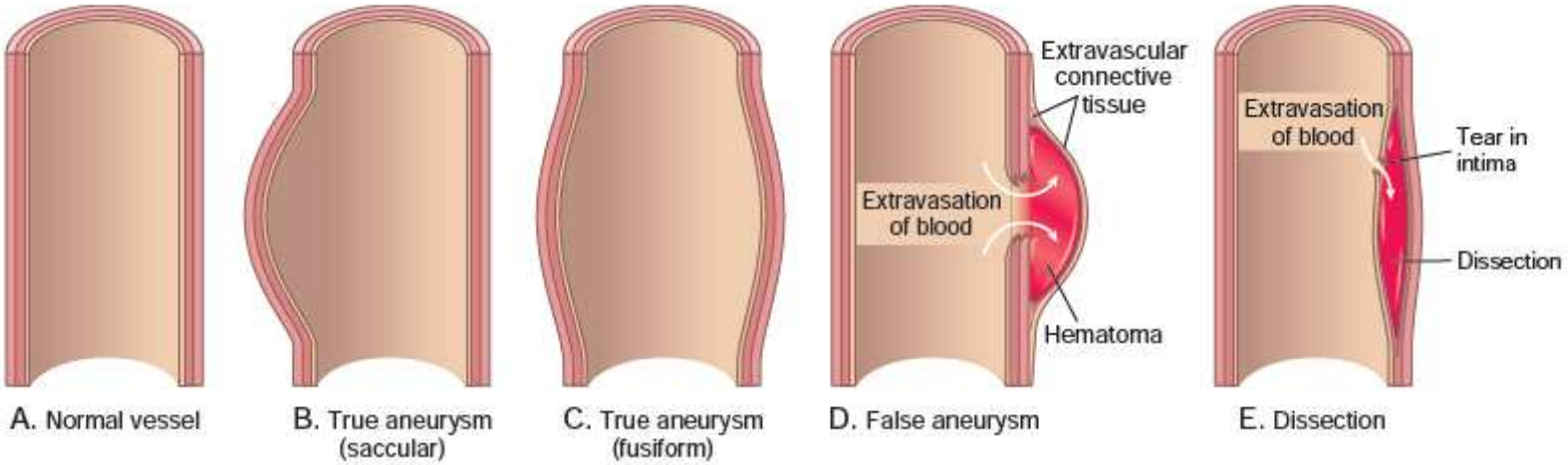


Figure 11-18 Aneurysms. **A,** Normal vessel. **B,** True aneurysm, saccular type. The wall focally bulges outward and may be attenuated but is otherwise intact. **C,** True aneurysm, fusiform type. There is circumferential dilation of the vessel, without rupture. **D,** False aneurysm. The wall is ruptured, and there is a collection of blood (hematoma) that is bounded externally by adherent extravascular tissues. **E,** Dissection. Blood has entered (dissected) the wall of the vessel and separated the layers. Although this is shown as occurring through a tear in the lumen, dissections can also occur by rupture of the vessels of the vasa vasorum within the media.

Abdominal aorta aneurysm

- Occurs principally in men in their 50's
- Tobacco is an associated risk factor
- May have vague associated abdominal pain.
- There is a large pulsatile immobile mass usually located above the umbilicus.
- Distal pulses may be diminished.

Abdominal aorta aneurysm complications

- Obstruction of a vessel branching off from the aorta, resulting in ischemic injury to the supplied tissue
- Embolism from atheroma or mural thrombus
- Impingement on an adjacent structure, for example, compression of a ureter or erosion of vertebrae

Abdominal aorta aneurysm causes

- (1) Increased metalloproteinase expression leads to degradation of extracellular matrix components of arterial wall.
- (2) 5-10% in younger patients (inflammatory)
- Back pain and elevated CRP prominent
- Thought to be localized immune destruction of wall.
- Prominent lymphoplasmacytic infiltrates
- Dense peri-aortic scar that may extend to retroperitoneum
- (3) IgG_4 related disease
- (4) Mycotic aneurysm

Abdominal aorta aneurysm rupture

- Presents with acute abdominal or flank pain.
- May have syncope.
- Orthostatic hypotension, and is a late finding in rupture.
- Usually into peritoneal cavity or retroperitoneal tissues
- Absence of blood in the stool common.
- Rupture into the duodenum is unlikely
- Dissection of the media is also a complication.

Abdominal aorta aneurysm

- Aneurysm rupture is related to the size of the aneurysm.
- Aneurysms <4cm diameter have a <1% 5 year rupture rate; 4-6cm, 16%; >6cm, 31%.
- For those with aneurysms >6m, the 5 year survival rate is 54% if not surgically repaired.
- The rate of expansion is faster for larger aneurysms
- 0.8cm/yr for aneurysms >5cm diameter as opposed to 0.2cm/yr for those <5cm diameter

Abdominal aorta aneurysm

- For palpation of abdominal aneurysm, in age group >50 years old, sensitivity 57% if <4cm, 97% if >4cm.
- Palpable mass unlikely if aneurysm has ruptured.
- High inter-observer reliability (surgeons, nurses, patients) in high prevalence situation; positive likelihood ratio 12.
- If low prevalence situation, age <50 years old, sensitivity 35% (positive predictive value, LR+, 43%)
- Ultrasound highly accurate.
- 30% risk of paraplegia with surgical repair

Histopathology

- Usually positioned below the renal arteries and above the bifurcation of the aorta
- Can be saccular or fusiform
- Severe atherosclerosis with destruction and thinning of the underlying aortic media
- Frequently contains a bland, laminated, poorly organized mural thrombus
- May affect renal or inferior mesenteric arteries by direct extension or by occluding the vessel opening

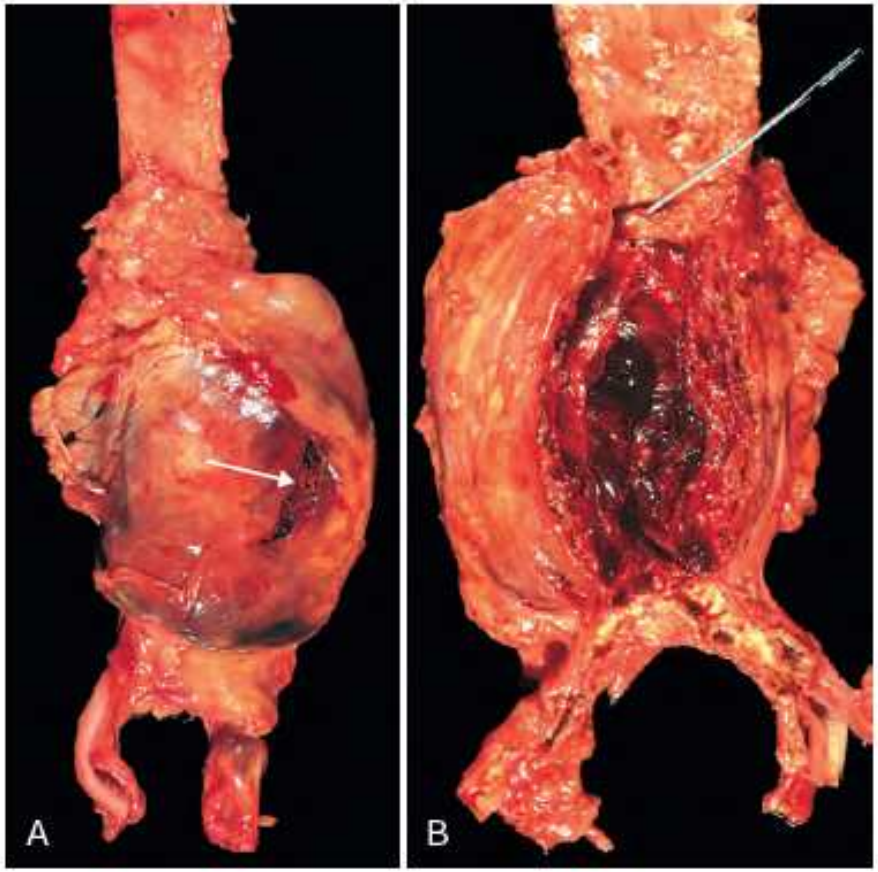
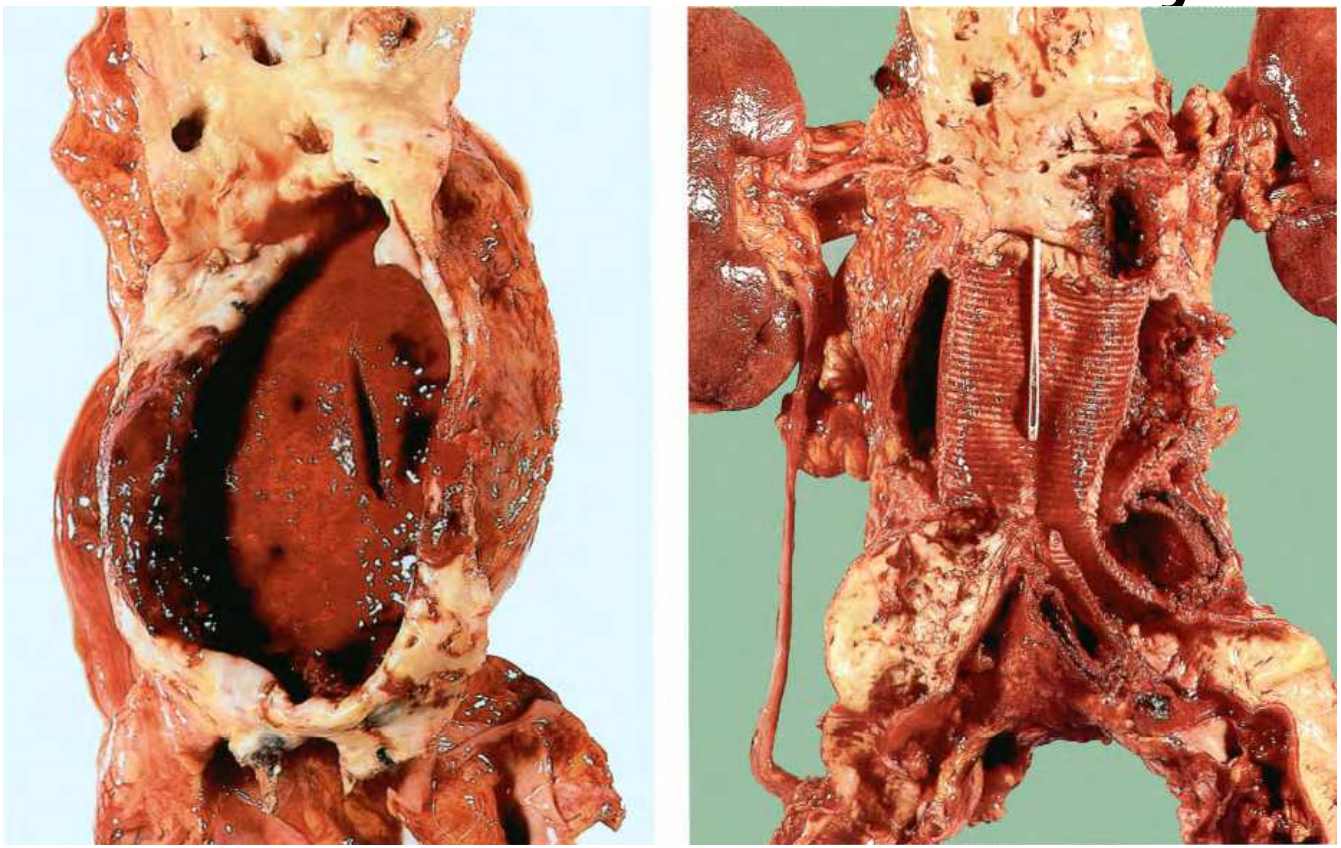


Figure 11-20 Abdominal aortic aneurysm. **A,** External view, gross photograph of a large aortic aneurysm that ruptured (rupture site is indicated by the *arrow*). **B,** Opened view, with the location of the rupture tract indicated by a probe. The wall of the aneurysm is exceedingly thin, and the lumen is filled by a large quantity of layered but largely unorganized thrombus.

Abdominal aortic aneurysm



Left: The ruptured aortic abdominal aneurysm is filled with thrombus. Right: Dacron graft repair of aortic abdominal aneurysm. The suture lines are all intact. The aorta and the common iliac arteries show severe atherosclerosis.

Sheppard, MN, Herrington, CS, "The Cardiovascular System," in Herrington, CS (ed), Muir's Textbook of Pathology, 15th edition. 2014. CRC Press. Boca Raton, Florida. Figs. 1.14 and 1.15

Thoracic aortic aneurysm

- Presentation includes:
- (1) respiratory difficulties due to encroachment on
- the lungs and airways
- (2) difficulty in swallowing due to compression of the esophagus
- (3) persistent cough due to compression of the recurrent laryngeal nerves
- (4) pain caused by erosion of bone (i.e., ribs and vertebral bodies),

Thoracic aortic aneurysm

- (5) cardiac disease as the aortic aneurysm leads to aortic valve dilation with valvular insufficiency or narrowing of the coronary ostia causing myocardial ischemia
- Most patients with syphilitic aneurysms die of heart failure secondary to aortic valvular incompetence
- (6) rupture.

Aortic dissection

- An aortic dissection usually initiates with an intimal tear.
- Blood separates the laminar planes of the media to form a blood-filled channel within the aortic wall.
- Usually between middle and outer thirds
- Usually ruptures through adventitia
- Massive hemorrhage or cardiac tamponade
- Occasionally re-enters lumen by second tear
- Dissection is unusual in the presence of substantial atherosclerosis or other cause of medial scarring

Aortic dissection

- In the vast majority of spontaneous dissections, the tear occurs in the ascending aorta, usually within 10 cm of the aortic valve
- 60% type A dissections
- Occur in ascending aorta proximal to subclavian artery
- Type B dissections occur distal to subclavian artery
- The dissection can extend retrograde toward the heart as well as distally

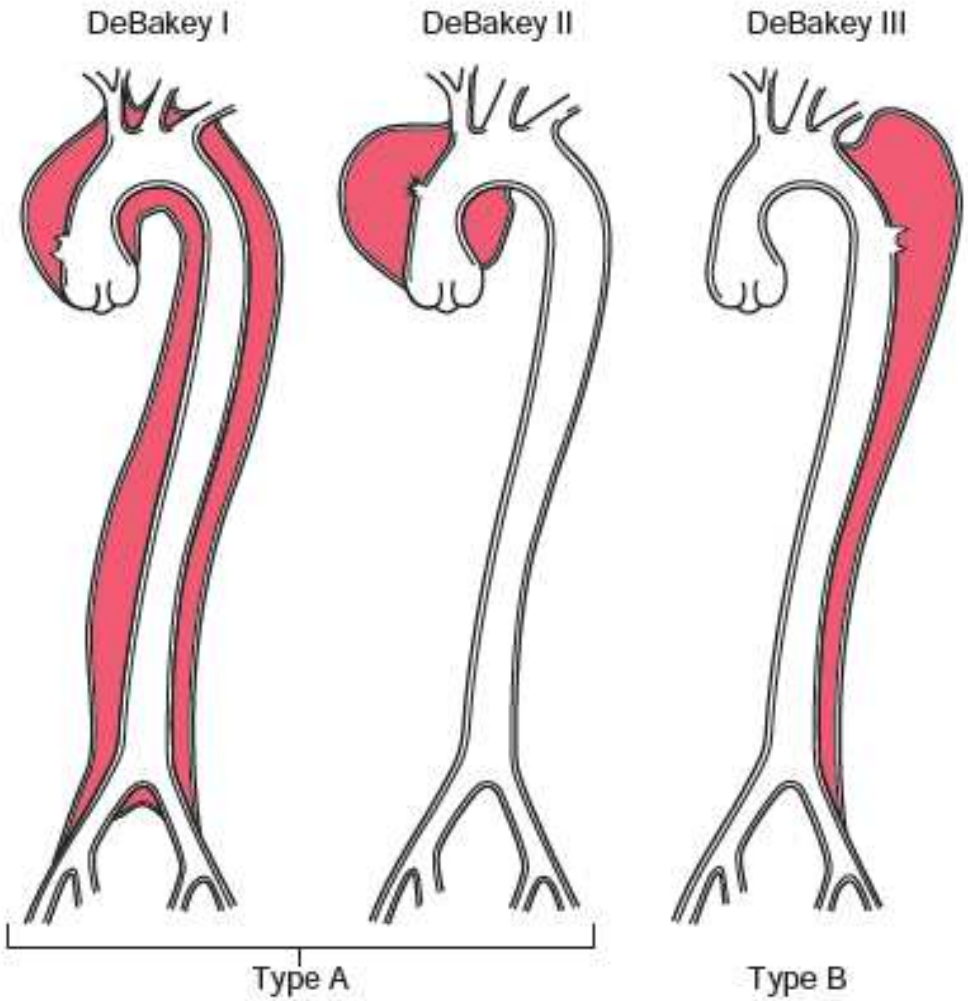


Figure 11-22 Classification of dissections. Type A (proximal) involves the ascending aorta, either as part of a more extensive dissection (DeBakey I) or in isolation (DeBakey II). Type B (distal or DeBakey III) dissections arise after the take-off of the great vessels. Type A dissections typically have the most serious complications and greatest associated mortality.

Aortic dissection

- Hypertension is major risk factor
- 90%, hypertensive men
- 40-60 years of age
- Cystic medial degeneration found
- If in younger individuals, usually in patients with connective tissue disorders
- Consider if young hypertensive patient has chest pain following cocaine use.
- CT or transesophageal echocardiography
- Type A managed surgically.
- 40-60% 10 year survival

Thoracic aortic dissection

- Contralateral pulse deficit in patients presenting with sudden tearing or ripping chest pain
- A widened mediastinum on chest x-ray
- Compatible with a diagnosis of thoracic aortic dissection (LR+, 66).
- The presence of a focal neurologic deficit also increases the likelihood.
- The absence of any two of the three makes the diagnosis unlikely (LR-, 0.6)

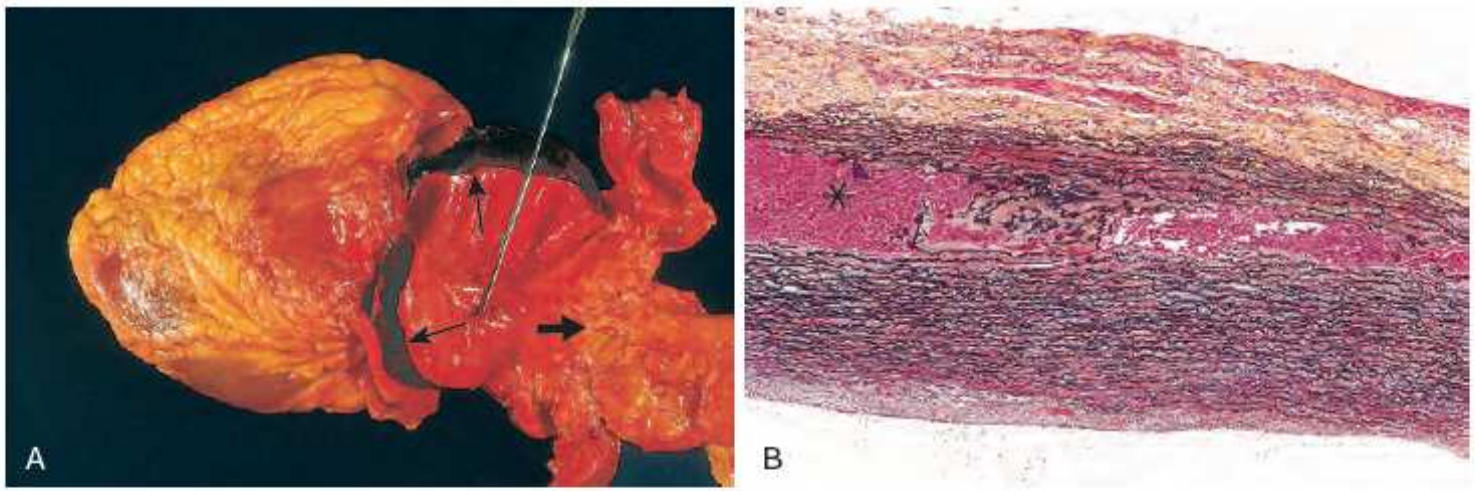
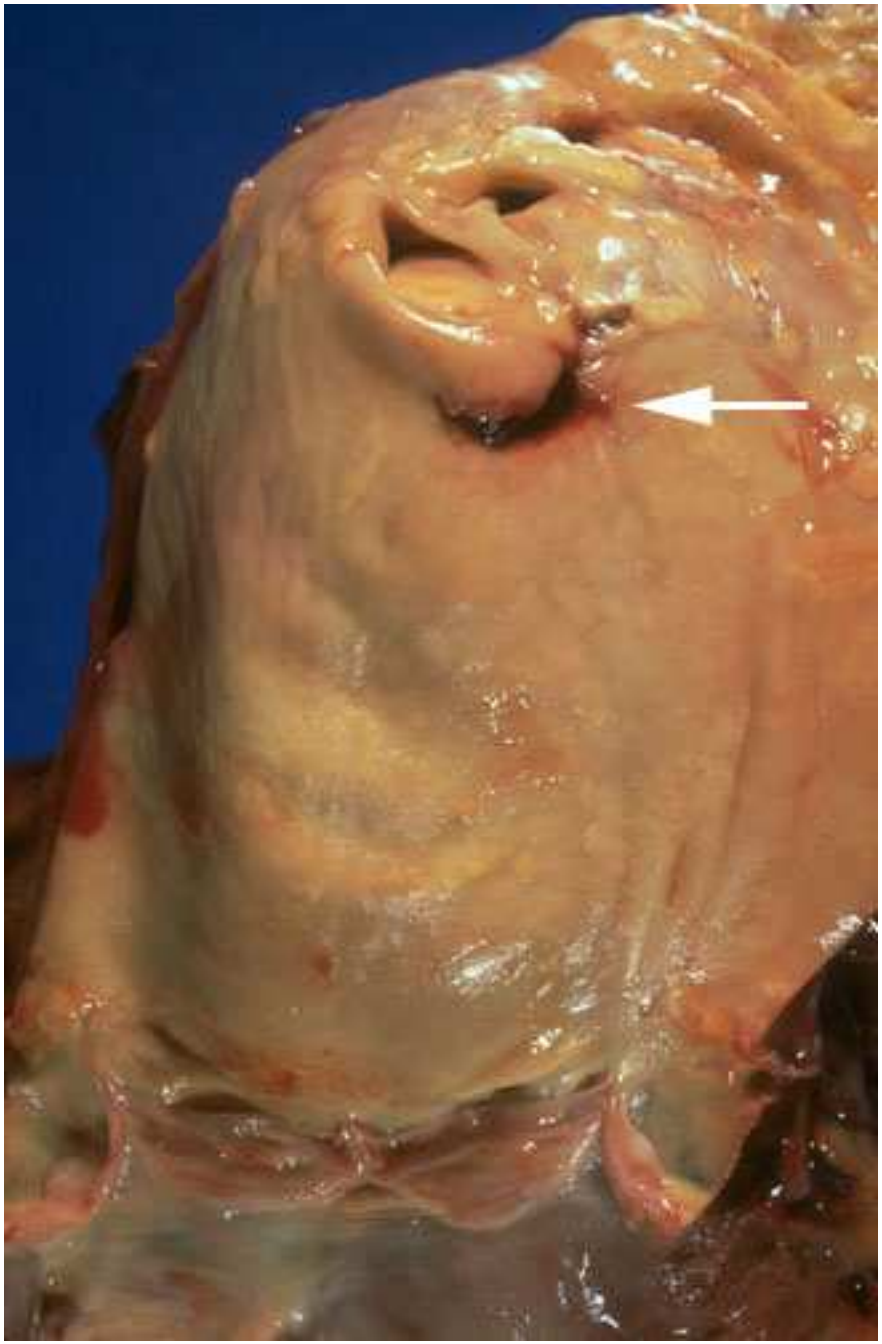


Figure 11-21 Aortic dissection. **A,** Gross photograph of an opened aorta with proximal dissection originating from a small, oblique intimal tear (probe), allowing blood to enter the media and creating a retrograde intramural hematoma *(narrow arrows)*. Note that the intimal tear has occurred in a region largely free of atherosclerotic plaque and that propagation of the intramural hematoma distally is arrested where atherosclerosis begins *(broad arrow)*. **B,** Histologic view of the dissection demonstrating an aortic intramural hematoma *(asterisk)*. Aortic elastic layers are black and blood is red (Movat stain).

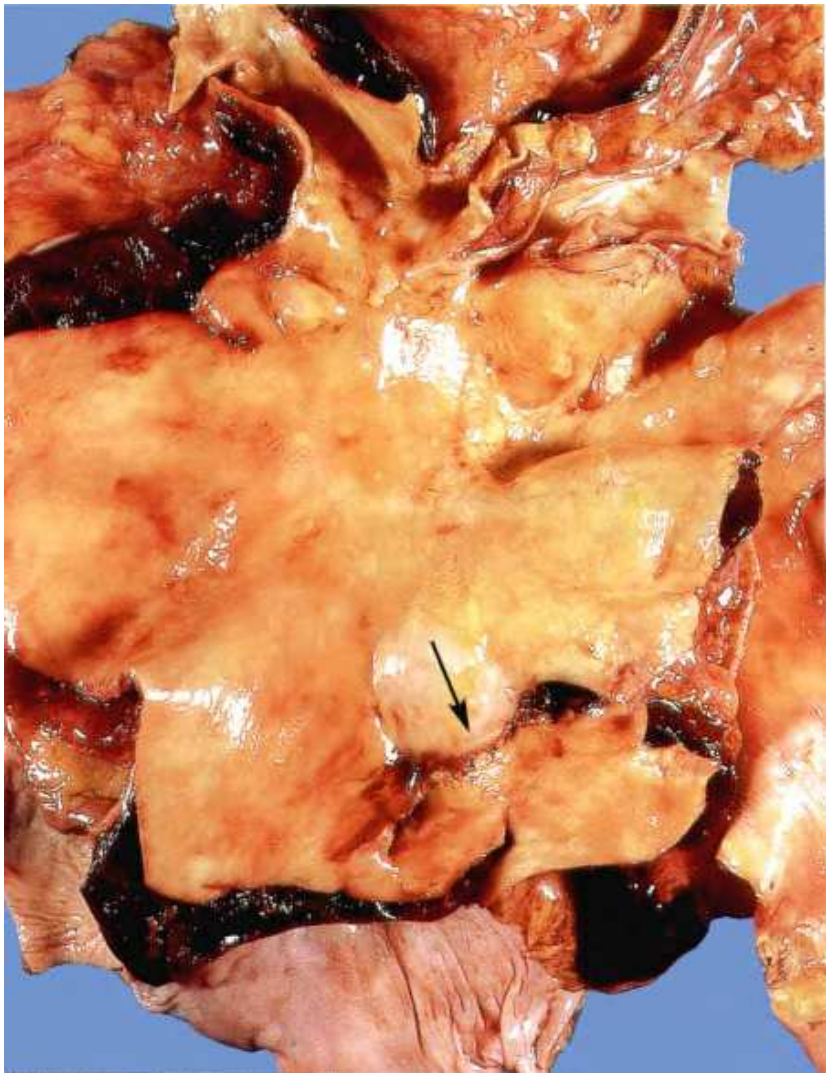


Thoracic aortic dissection

There is a tear (arrow) located 7 cm above the aortic valve and proximal to the great vessels in this aorta with marked atherosclerosis.

https://webpath.med.utah.edu/CVHTML/CV158.html

Thoracic aortic dissection



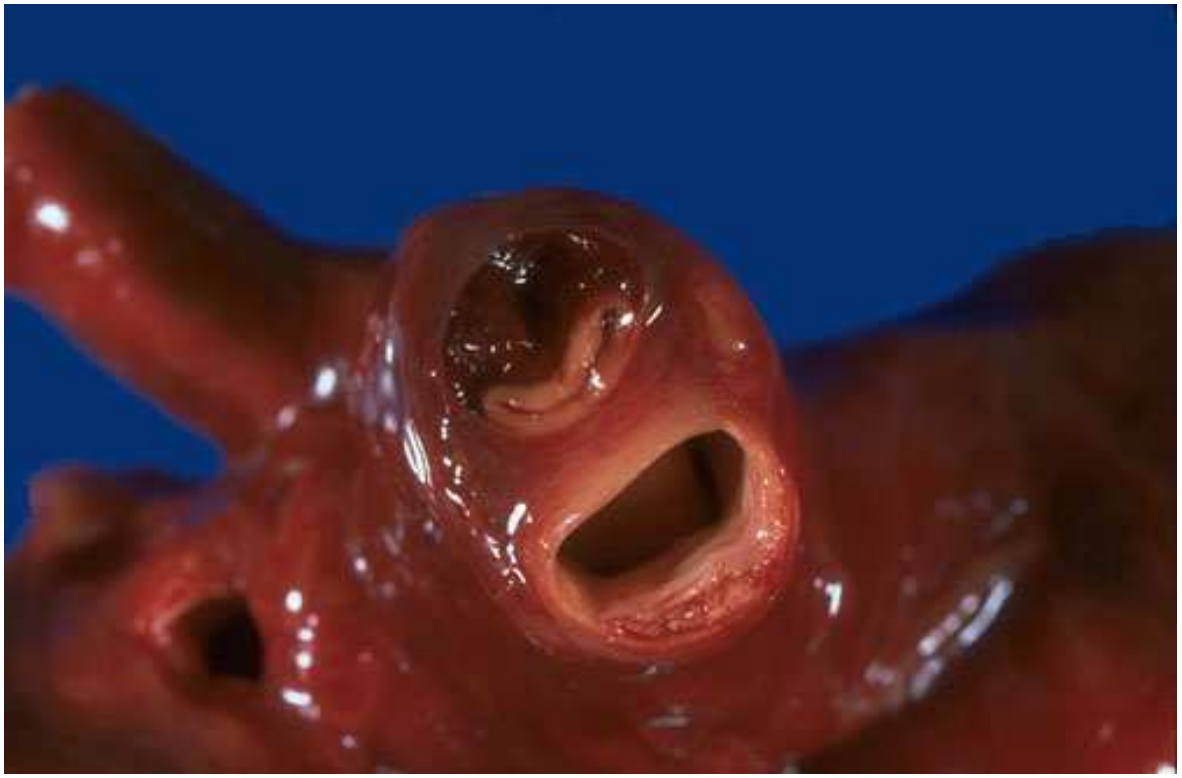
The wall of the arch of the aorta has split longitudinally and blood fills the false channel. This can be seen in the top and bottom of the picture. There is a transverse tear in the intima (arrow). This connects with the longitudinal split in the wall of the aorta. The dissection is extending into the innominate and left common carotid arteries.

Sheppard, MN, Herrington, CS, "The Cardiovascular System," in Herrington, CS (ed), Muir's Textbook of Pathology, 15th edition. 2014. CRC Press. Boca Raton, Florida. Fig. 1.14

Carotid artery dissection

- Patients with aortic dissection may have symptoms of severe chest pain (for distal dissection) or may present with findings that suggest a stroke (with carotid dissection) or myocardial ischemia (with coronary dissection).
- Leading cause of stroke in young adults.
- Spontaneous
- Increased incidence of carotid artery dissection in pregnancy.
- May present with refractory headache.

Carotid artery dissection



The right carotid artery is compressed by blood dissecting upward from a tear with aortic dissection. Blood may also dissect to coronary arteries.

https://webpath.med.utah.edu/CVHTML/CV161.html