Atherosclerosis

History of Presenting Illness : these people will present as exercise limitation

PAIN!! WORST EVER → like giving birth through the chest wall.
→ Radiates in characteristic path, see Mr. Sarich
ANGINA (essentially, claudication of the heart)
Shortness Of Breath
CLAUDICATION: pain assoc. with exercise
Loss of sensation @ distal limb

There may not be pain- 20% of MIs are silent.
Pain is the last sign of MI

Differential Diagnoses

Claudication:

- Aneurysms, Abdominal
- Ankle, Soft-tissue Injures
- Back Pain, Mechanical
- Deep Venous Thrombosis and Thrombophlebitis
- Lumbar (Intervertebral) Disk Disorders
- Thrombophlebitis, Septic
- Thrombophlebitis, Superficial
- Trauma, Peripheral Vascular Injuries

Ischaemic Heart Disease:

- Angina Pectoris
- Atherosclerosis
- Buerger Disease (Thromboangiitis Obliterans)
- Cardiac Catheterization (Left Heart)
- Cardiomyopathy, Dilated
- Cardiomyopathy, Hypertrophic
- Coronary Artery Anomalies
- Coronary Artery Atherosclerosis
- Coronary Artery Vasospasm
- Diabetes Mellitus, Type 1
- Diabetes Mellitus, Type 2
- Giant Cell Arteritis
- Heart Failure
- Hypercholesterolemia, Familial
- Hypercholesterolemia, Polygenic
- Hypertension
- Hypertensive Heart Disease
- Hypertriglyceridemia
- Kawasaki Disease
- Myocardial Infarction
- Myocarditis
- Percutaneous Transluminal Coronary Angioplasty
- Pericarditis, Acute
- Right Ventricular Infarction
- Treadmill and Pharmacologic Stress Testing
- Unstable Angina
- Wolff-Parkinson-White Syndrome

Pertinent Findings on History

Ask about risk factors:

- Personality (type A)
- SMOKING
- Hypertension → last BP measurement
- Hyperlipidaemia
- Previous arterial disease
- Diabetes (!!)
- Homocysteinaemia

EARLY : pain on exercise, relieved by rest;
MIDDLE: pain @ rest, relieved by exercise
("burning numbness", = fibrinomyositis)
LATE: ulceration and rampant gangrene

Ask about duration, progression, severity: "CLAUDICATION DISTANCE"

Findings on Examination : bruits, bruits everywhere!

The affected limb will be …

- Pale
- Cold
- Atrophied
- Hairless
- Lacking of pulse
- Cyanotic
- Brittle nails
- Shiny skin
- Poorly healing injuries
- There may be **ISCHAEMIC ULCERS** (like diabetic neuropathy, reddy-brown gangrenous indurated lesions) But they will not be associated with varicose veins (i.e not varicose

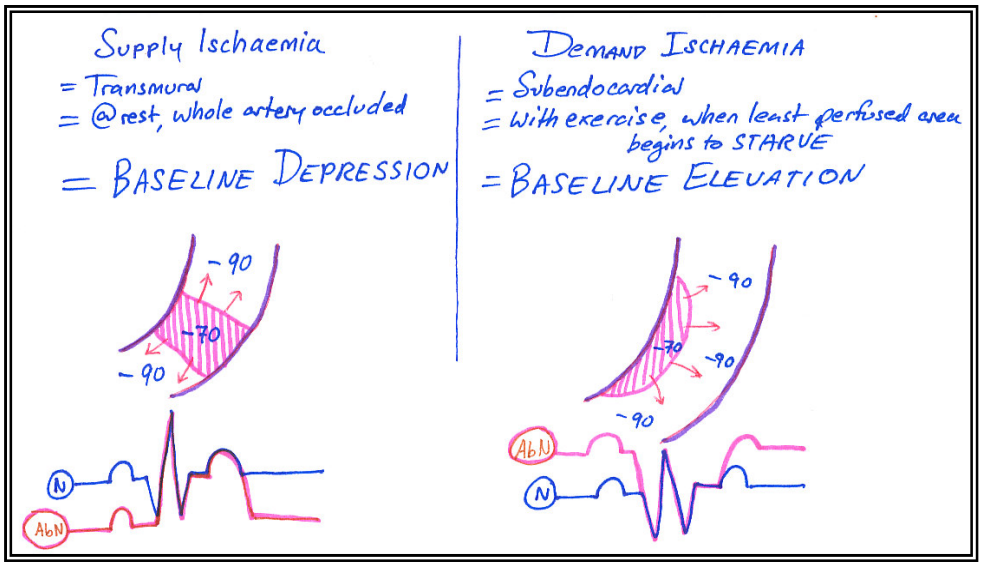
THERE MAY BE A DIFFERENCE IN BLOOD PRESURE BETWEEN THE LOWER AND UPPER LIMBS (ABI)
~1.0 = normal;
~0.9 = claudicated;
~0.5 = leg about to fall off

INVESTIGATIONS: Ischaemic Heart Disease + Angina

LAD = V1-V4
LCX=V6, aVL
RCA=II, III, aVF

ECG: the KING of tests

INFARCT LOCALISATION: ST changes →



For ANGINA:

Can do an exercise tolerance test
Eg. treadmill; watch those ST segments rise.
SEE ABOVE for localisation of the occluded artery

USEFUL DEFINITION

"UNSTABLE" angina: Severe and unpredictable angina in which the severity, frequency, or length of angina attacks suddenly increases

Angiography/plasty is the QUEEN of MI assessment/management

→not only can one SEE the occluded coronary artery, but one is also in a unique position to do something about it:
thus usually an MI will be wheeled straight into the catheter lab

Echocardiography

Major role is in determining the degree of heart failure which is usually associated with ischaemic heard disease.
Eg.: hypomotility of ventricular wall from previous MI
(useful if performed at rest and then with mild exercise)

CKMB serial measurements: @ 8, 16, 24 hrs

→ creatine kinase sub-type specific to the myocardium

LIPID STATUS: check LDL, HDL, (important risk factor)

BLOOD SUGAR: same reason

CHEST X-RAY: looking for cardiomegaly and congestive HF signs

INVESTIGATIONS: Peripheral Vascular Disease

STENOSIS is most commonly in the femoro-popliteal arterial segment

CHEAPEST AND MOST USEFUL TEST:
WALK with the patient UNTIL THE PAIN APPEARS. →confirm nature of pain
Examine after the walk. →**palpation and auscultation of the arterial tree of the lower limbs**
Then…

continuous wave Doppler to detect the presence or absence of flow in distal segments

- usually with segmental measurements of the systolic arterial pressure down the limb.
- coupled with treadmill exercise,
- with systolic measurements performed before and after exercise until the ankle arterial pressure returns to the pre-excise level.
- These may be compared with the brachial artery systolic pressure to generate a ratio called the ankle/brachial index.

angiography by direct femoral puncture
or via intra-arterial catheters) →to see patent arterial segments
arterial duplex scanning of the lower limb arteries) → for flow in open vessels
=non-invasive and almost as accurate as arteriography
= able to assess flow velocities to determine whether an arterial stenosis contributes significantly to the symptomatic limitation of flow. I.E. whether a patient is suitable for balloon angioplasty

SCOPE THE FUNDUS!! → for evidence of hypertensive retinopathy
→ the fundus of the eye is the only place where you can non-invasively visualise the blood vessels

Disease Definition

Widespread atherosclerosis leading to narrowing of coronary and peripheral arteries resulting in ischaemia and thereby pain, on exertion

Management: for MI see 1.03; PERIPHERAL VASCULAR DISEASE + ANGINA

Simple goals:

Reduce risk of sudden death

- **Nitrates**
- **Beta blockers**
- Perhexiline if all else fails (v. toxic, must avoid)

reduce risk factors + improve prognosis

- **quit smoking!! → best thing ever**
- **Revascularise the ischaemic limbs and heart ..so that the patient can**
- **Start exercising without irritating claudication limitations**
- **Reduce weight**
- **ASPIRIN (antithrombosis) = live twice as long**
- **Lower lipids with STATINS (reduce severity of atheromae)**

Prognosis: VERY BAD.

In asymptomatic patients, the presence of exercise-induced ST-segment depression predicts **a 4- to 5-fold increase in cardiac mortality rate** compared to patients without this finding.

In general, the more acute the ischemia, the greater the amount of ischemic myocardium; the lesser the extent of coronary collateral vessels, the greater the severity of CAD and the smaller the CFR, and the greater the degree of LV dysfunction; the more pronounced these effects, the worse the prognosis.

- **Survivors of MI exhibit a poorer prognosis.**
- They have a 1.5- to 15-times higher risk of mortality and morbidity
- and are at higher risk for subsequent MI, + same for fatal and near-fatal arrhythmias as a result of myocardial ischemia.

- Within a year of MI, 25% of men and 38% of women die.
- Within 6 years, 18% of men and 34% of women have a second MI, 7% of men and 6% of women experience sudden death, 22% of men and 46% of women are disabled with CHF, and 8% of men and 11% of women have a stroke.

Epidemiology

Atherosclerotic coronary heart disease (CHD) causes approximately 500,000 deaths in the United States each year, ie, about 1 in 5 deaths overall.

- Roughly 6.3 million Americans are believed to experience angina.
- An estimated 350,000 new cases of angina occur every year.
- More than 12 million Americans had a history of MI and/or angina pectoris in the year 2000.
- About every 29 seconds, an American has a coronary event
- about every minute someone dies from one.
- Approximately 14 million people alive today have coronary disease: 6.5 million males and 7.5 million females.
- Roughly 1.5 million Americans have new or recurrent acute MIs each year, 40% of these individuals die as a result.
- From 1987-1997, however, the death rate from CHD declined 24.9%.

- **Internationally:** *International incidence, especially in the developed countries, echoes that observed in the United States*

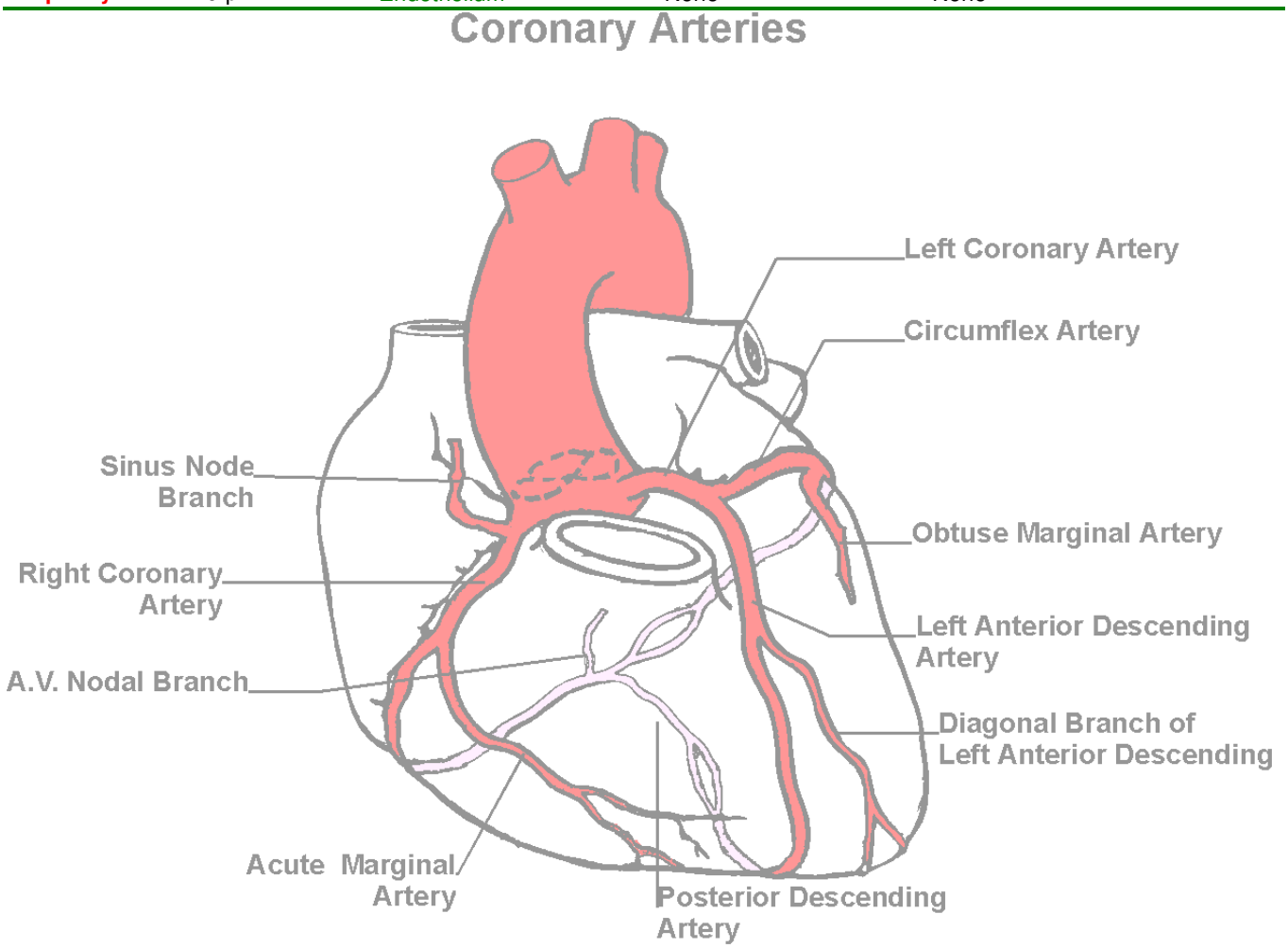
Relevant anatomy: Gross and Fine Anatomy of Blood Vessels

Histology of the Arteries

- ALL ARTERIES HAVE the same 3 LAYERS:
- The **tunica intima** consists of a single layer of endothelial cells that rest on a basal lamina and loose connective tissue.
- The **tunica media** consists primarily of layers of circumferentially arranged smooth muscle cells.
- The **tunica adventitia** consists of longitudinally arranged collagenous tissue and some elastic fibres.
- **The tunica adventitia gradually merges with the loose connective tissue surrounding the vessels.**

Characteristics of Blood Vessels

Vessel	Diameter	Tunica Intima	Tunica Media	Tunica Adventitia
Elastic artery	>1 cm	• Endothelium • Connective tissue • Smooth muscle	• Smooth muscle • Elastic lamellae	• Connective tissue • Elastic fibres • **Thinner than media**
Muscular Artery	2-10 mm	• Endothelium • Connective tissue • Smooth muscle • Prominent internal elastic membrane	• Smooth muscle • Collagen fibres • Relatively little elastic tissue	• Connective tissue • Some elastic fibres • **Thinner than media**
Small artery	0.1-2 mm	• Endothelium • Connective tissue • Smooth muscle • Internal elastic membrane	• Smooth muscle (8-10 cell layers) • Collagen fibres	• Connective tissue • Some elastic fibres • **Thinner than media**
Arteriole	10-100 µm	- Endothelium • Connective tissue • Smooth muscle	• Smooth muscle (1-2 cell layers)	• Thin, ill-defined sheath of connective tissue
Capillary	4-10 µm	• Endothelium	• None	• None



Pathogenesis of Atheroma 5.04

ARTERIAL BRANCH POINTS

-are areas of turbulence and thus **Chronic HIGH SHEAR STRESS**

HYPERTENSION

HYPERLIPIDAEMIA

High cholesterol increases endothelial production of SUPEROXIDE and O_2 FREE RADICALS

OF INTEREST:
Calcification of atheromae occurs when necrotic debris yield short side chains (protein breakdown products) which bind normally circulating Ca++ --THIS IS NOT what happens to the ligaments of the elderly, or in new bone formation

SHEAR STRESS @ endothelium induces:

- **Increased permeability**
- **Adhesion molecule expression (ICAM-1) and (VCAM-1)**
- **Cytokine production**
- **Increased endothelial cell turnover**

DEACTIVATION OF Nitric Oxide
thus no smooth muscle relaxation: Impaired endothelial cell-mediated dilatation leads to
→ **CHRONIC NARROWING**
which contributes to shear stress

LIPOPROTEINS penetrate into the intima, thanks to increased endothelial permeability

OXIDATIVE MODIFICATION
Of lipids by oxygen radicals converts lipid into
OXIDISED (modified) LDL

Which…

- **Induces ADHESION MOLECULES**
- Is **chemotactic for macrophages**
- **IMMOBILISES macrophages**
- Is **readily ingested by macrophages**
- Stimulates release of **growth factors and cytokines**
- **Is CYTOTOXIC to endothelial cells and smooth muscle cells**

When Glycated in diabetics, it turns IMMUNOGENIC, inducing antibody production to oxidised lipoproteins

MACROPHAGES:

- **are attracted by oxidised LDL**
- **attach to endothelium** via ICAM and VCAM proteins
- become **IMMOBILISED**
- **begin to ingest the oxidised lipoprotein**

…AND DIFFERENTIATE INTO FOAM CELLS
which…

- **Produce IL-1**
- **Produce TNF-alpha**
- **Produce MCP-1** Monocyte Chemoattractant Protein-1
- **Produce Tissue Factor**
- **Produce PDGF** SM cells **producing IL-6** also attract lymphocytes which are present in atheromatous lesions

FOAM CELL AGGREGATES appear grossly as FATTY STREAKS which are STILL REVERSIBLE !!

PLATELETS adhere to areas of endothelium which are denuded by shear stress and other injury

INCREASED MONOCYTE CHEMOTAXIS

TF is thrombogenic if plaque ruptures

ACTIVATED PLATELETS, MACROPHAGES and ENDOTHELIAL CELLS RELEASE PDGF, FGF, TGF-α
All of which cause angiogenesis

SMOOTH MUSCLE CELLS proliferate under the influence of these factors; –**BECOME TRANSFORMED** into non-contractile subtypes which in every way resemble foam cells

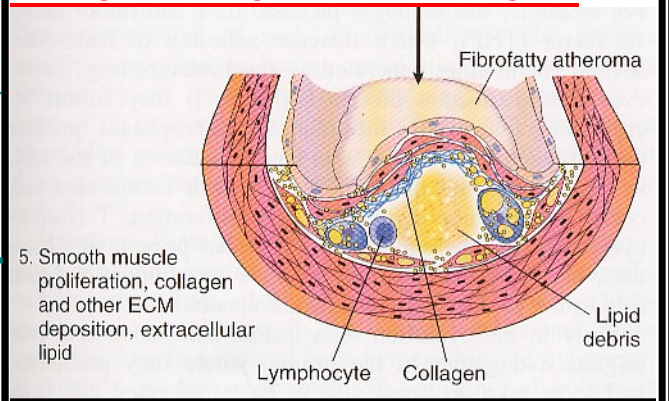
FIBROBLASTS are attracted to the atheroma; → begin to **build COLLAGEN**
Thus: a **fibrous cap** forms over the lesion and is degraded by macrophage proteinases

NECROSIS occurs due to the direct toxicity of oxidised LDL: THUS: the atheroma has a soft necrotic core

ANTIBODIES and hence COMPLEMENT accumulates beneath the fibrous cap of the atheroma, contributing to **NECROSIS**

Lymphocytes release IFN γ Which weakens the fibrous cap by inhibiting collagen synthesis & repair by SM cells and fibroblasts

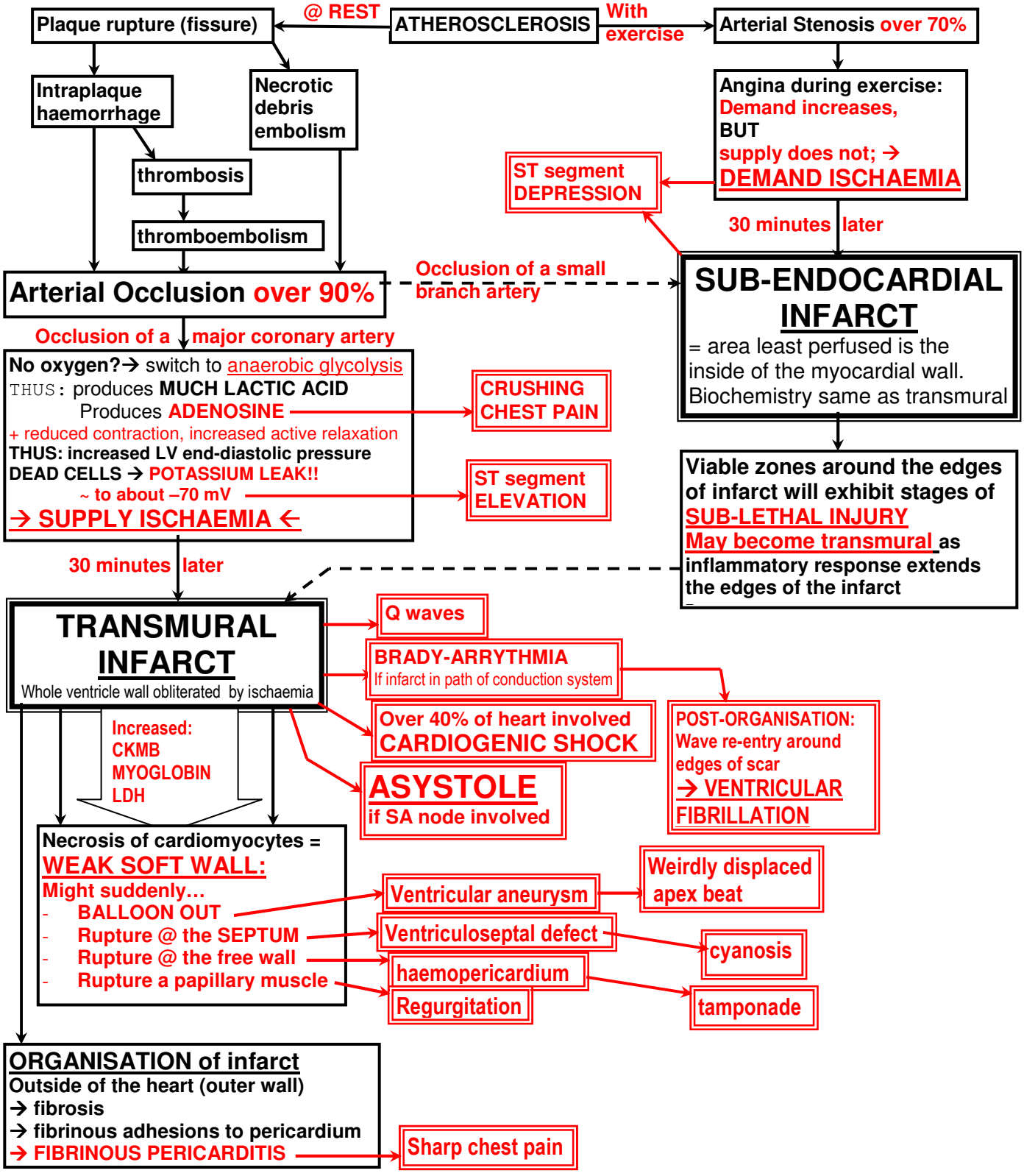
MATURE FIBROFATTY ATHEROMA



No Longer Reversible by lipid-lowering therapy

QUITE SOFT AND LIKELY TO FISSURE!
→ leading to a **FATTY EMBOLUS** impacting somwhere downstream of the lesion
→ resulting fissure (mild in exposes intimal colagen, which attracts platelets and promotes **THROMBOGENESIS**
→ resulting THROMBUS aggravates the atheroma, accelerates its growth and also threatens to break off and embolise.
→Intraplaque Haemorrhage may occlude the vessel without thrombosis or embolism

Pathophysiology of Ischaemia: preliminary mechanism 5.04



Pathophysiology of Ischaemia 5.04

(ischein=to suppress, haemia=blood).

Demand ischaemia vs. Supply ischaemia: exercise vs. rest.

demand ischaemia typically occurs during exercise in patients with a coronary stenosis of 70% or greater and is quickly relieved by rest.
Supply ischaemia occurs at rest when an artery occludes or suddenly develops a stenosis of 90% or greater.

Myocardial ischaemia = insufficient blood flow to meet the metabolic demands of the beating heart
As myocardial O_2 demand increases, it must be parallelled by an increase in myocardial blood flow,
- because coronary arteriovenous O_2 extraction is near maximal at rest.

The major determinants of myocardial O_2 consumption are:
- Heart rate
- Left ventricular (LV) wall stress
- Contractility.

70% of the lumen obstructed = flow limitation with exercise
a stenosis of 90% will limit flow at rest.
Stenoses of <70% lumen diameter do not usually limit flow during exercise.

POUSEILLE's EQUATION:
Reduce radius by half:
Flow is reduced 16 times!

COMPLETE OCCLUSION FOR 30 min. ➔ myocardial infarction and cell death

metabolic and physiological changes in the myocardium:
- Metabolism switches from aerobic utilisation of fatty acids…
- to **anaerobic glycolysis with production of lactic acid.**
- ATP production falls, and this causes failure of both contraction and active relaxation, which can result in **elevation of LV end-diastolic pressure and breathlessness**.
- **K^+ leaks out of cells, raising resting membrane potential** and reducing action potential size and duration.
- This produces characteristic ECG changes:
- **ST segment depression with subendocardial ischaemia and**
- **ST segment elevation with transmural ischaemia.**
- Elevation and depression of ST segments are relative to the isoelectric segments in the TP and PQ periods.

CHEST PAIN = LATE EVENT of M.I.
The pain producing stimulus is probably **adenosine,** from breakdown of ATP
the sensation is carried by **sympathetic afferents which synapse between spinal segments C8 and T4**
producing **referred pain in the retrosternal area, typically radiating to the left arm**.
Many attacks of ischaemia, however, are not accompanied by anginal pain (**silent ischaemia).**

COMPLICATIONS OF ISCHAEMIC HEART DISEASE 5.04

Arrhythmias: conduction disturbances
- acute stage,
- infarcts which involve the conduction system usually produce bradyarrhythmias
  eg. transmural post. left ventricle wall infarct
- **tachyarrhythmias result from myocardial irritability or re-entry.**
- **late after infarction, ventricular tachcardia and fibrillation** result from re-entry around the edges of scar,
- = are a major cause of sudden death.

Left ventricular dysfunction:
This may lead **to left-sided cardiac failure, pulmonary congestion and oedema**.
transmural infarct involving 40% of the left ventricular wall =
- **profound ventricular dysfunction,**
- **acute "pump failure"**
- **cardiogenic shock.**

Rupture of the myocardium:
Infarcted myocardium undergoes softening especially during the acute inflammatory response to the necrosis.
= RUPTURE OF:
- The **free or external ventricular wall**. ➔ Haemopericardium will result from escape of blood from the left ventricle.
- The **interventricular septum**. ➔ Shunting of blood between the ventricles will now be possible.
- The **papillary muscle** ➔ acute onset of mitral regurgitation

Mural thrombosis:
stasis of blood due to ventricular hypokinesis or endocardial injury in the area of infarction.
Patients with myocardial infarction are at high risk of development of hypercoagulability of blood. They are predisposed to the development of deep venous thrombosis and pulmonary embolism.

Mostly, myocardial infarction will commence in the subendocardial region which is the least well-perfused part of the myocardium. However within a few hours, this **infarct can progress along a wavefront of necrosis to become transmural**. This wavefront necrosis may be modified by prompt thrombolysis and coronary reperfusion.

- transmural myocardial infarction ➔ acute fibrinous pericarditis within a few days
- **Infarct extension.**
  - The zones bordering an infarct = still viable, but exhibit changes of sublethal injury reflecting a lesser degree of ischaemic injury.
  - These zones are unstable due to ischaemia
  - in the days or weeks following the original infarct there may be extension of necrosis into these adjoining areas.

Cardiac remodelling.

- = infarct expansion which begins as early as within 24 hours after occurrence of infarction
- in which the **area of infarction undergoes disproportionate stretching and thinning**.
- further necrosis is not a prerequisite.
- A similar but less pronounced thinning and dilatation occurs in the adjoining non-infarcted region.
- This is due to rearrangement of myocytes or "cell slippage" with a reduction in layers of myocytes in the ventricular wall.

THUS the ventricle dilates,
its volume increases as do the stresses on its wall.
Such patients have higher mortality than those in whom remodelling is not observed because of **development of congestive heart failure and ventricular arrhythmias**.
It is believed **that remodelling may be modified by treatment which reduces preload or afterload stress** and that coronary reperfusion may also be beneficial.

PERSONALITY LINKS TO CORONARY ARTERY DISEASE 5.04

Linkages between personality and disease
personality is related to the development of disease and influences disease outcomes.
correlation does not equal causation.
Observed correlations may reflect a range of processes including:

(1.) direct causation;
(2.) reverse causation - where disease processes overtly or covertly influence aspects of personality functioning;
(3.) co-varying risk behaviours (behavioural third variables);
(4.) physiological third variables; and
(5.) research artefacts.

Personality refers to the patterns of cognitive, affective, and behavioural dispositions that characterise individuals. Personality patterns are thought to be relatively stable across time and context. For an overview of the main approaches to describing personality and theories of personality development, it will be useful to read chapter 14 of the Philipchalk and McConnell textbook. There is now fairly broad consensus that broad classifications of personality can be made on the basis of the "Big Five" traits: Extroversion (gregarious, enthusiastic, daring); Agreeableness (affectionate, gentle, empathic, cooperative); Conscientiousness (organised, reliable, persevering); Emotional stability (poised, calm, composed); Intelligence (intellectual, reflective, imaginative). Research is also attempting to identify more specific personality factors that contribute to effectiveness and adaptiveness, influencing sickness and health.

Personality and CHD (coronary heart disease)

Type A behaviour = significant risk factor for developing CHD.

key features = hostility, time urgency, impatience and competitiveness
Type A Behaviour does not markedly increase the risk of subsequent morbid events.

expressive hostility, **particularly antagonistic interactions with others (anger-out),** appears most strongly implicated with ongoing risk.
cynical mistrust, potential for hostility, and suppressed resentment (anger-in) have also been found to predict CHD mortality and morbidity.

Psychological hardiness: certain personality constellations may be associated with positive health outcomes
= *sense of control, commitment, and the viewing of change as exciting challenge rather than threat.*

Lifestyle modification in vascular disease 5.04

Lifestyle modification of people with vascular disease is **an essential component of secondary prevention.**

Cigarette smoking, poor dietary habit and inactivity are the major modifiable lifestyle risk factors.

- Giving out kits, leaflets, tapes, videos, phone support services provided by Government agencies, the National Heart Foundation, pharmaceutical firms and support groups.
- Enlisting the assistance of family members, carers and significant others, eg educating the wife if she is the family cook, giving the patient the responsibility to walk the dog.

Allied health professionals:

- Paramedical eg. dietitians, psychologists, physiotherapists.
- Medical specialist units eg shared care programs, smoking cessation clinics, cardiac rehabilitation units, obesity clinics.
- Community resources eg. National Heart Foundation, Public Health Units, Alcoholics Anonymous, smoking cessation programs eg Smokescreen.
- Commercial enterprises eg. Gutbusters, Weight Watchers, the local gym, various sporting and activity clubs.

Pharmaceutical agents:
These may be used as an adjunct to lifestyle modification eg

- Nicotine replacement therapy
- Dexfenfluramine hydrochloride as an appetite suppressant in a small subgroup of obese patients.

The person with vascular disease is most likely to achieve and maintain lifestyle changes under the care of a family General Practitioner because of the GP's unique and ongoing relationship with the patient

Drug therapy for stable effort angina 5.04

angina is merely a symptom of ischemia so drug therapy should not aim to merely relieve pain

➔ **must reduce ischemia.**

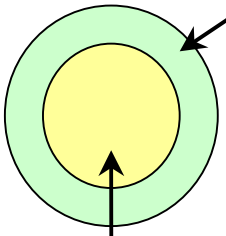
- **reducing the myocardial oxygen demand through blockade of the heart rate increase with exercise,**
- reduction in afterload and ventricular volume with a **vasodilator**.
- **Exercise training** may have a similar effect.
- The other approach to management of angina is to fix the obstruction to coronary blood flow with **bypass surgery or percutaneous coronary intervention.**

1. **Nitrates** . These drugs relax vascular smooth-muscle through a cyclic GMP mechanism and are both arterial and venodilators. They are also very effective if taken prophylactically just before angina.. Unfortunately long acting nitrates will produce tolerance within 24 hours unless a nitrate-free or nitrate-poor period of approximately 10 hours (often overnight) is provided in the regimen. Nicorandil is a novel nitrate with an additional potassium channel opening effect and may have a beneficial effect on prognosis.
2. **Beta-blockers** . These drugs reduce the heart rate and blood pressure at rest and during exercise and are very effective in patients with angina. They may also improve prognosis. The drugs most used are the beta-1 selective blockers (atenolol and metoprolol) = a lesser tendency to aggravate asthma or peripheral vascular disease
3. **Calcium entry blockers** . These drugs are arterial dilators and reduce blood pressure and afterload. Verapamil and diltiazem also have some heart rate slowing and myocardial depressant effects which may be useful in treatment of angina.. All drugs in this class can produce vasodilator side effects such as flushing, hypotension, and edema.
4. **Perhexiline** . This is a carnitine palmityl transferase-2 inhibitor which reduces the myocardial requirement for aerobic metabolism. The drug is very useful in refractory cases but blood levels must be monitored closely because a significant proportion of the population are genetically determined very slow drug metabolisers and will achieve very high blood levels which are both hepatotoxic and neurotoxic.
5. **Angiogenic drugs** . A number of angiogenic cytokines and genes are currently under investigation in patients with end-stage coronary artery disease. The hope is that angiogenesis will be induced to provide new collateral vessels an increase blood flow without the need for revascularisation.

Lipid Transport in the Bloodstream 7.05

Since they are not water soluble, the lipids must make alternative transport arrangements.
This involves being carted around in microscopic lipoprotein particles.

THE TYPICAL LIPOPROTEIN PARTICLE: is of SPHERICAL SHAPE, with a COAT and a CORE



OUTSIDE:

Made of **phosphatidyl choline**, aka. **LECITHIN**
This is a glycerol backbone with two fatty acids.
Being hydrophilic, the glycerol end of a lecithin molecule faces outwards, and the fatty acids face inwards, thus giving the lipoprotein a roughly spherical shape.
THIS IS A LIPID MONOLAYER
(not bilayer like in cell membranes, because the inside of a lipoprotein is made of hydrophobic lipids)
ALSO: the coat contains PROTEINS which give lipoproteins their name. These are responsible for targeting these proteins to specific cells.

INSIDE: **the TRANSPORTED LIPIDS:**
- **Triglycerides and Cholesterol esters**

EMBEDDED PROTEINS:
So-called "**Apolipoproteins**" because all lipid content has been leeched from them.

2 groups:
EXCHANGEABLE
- (can be swapped between two lipoprotein particles)
- **A1, A2, C2, E**

And
NON-EXCHANGEABLE
- (embedded forever in the lecithin layer)
- **B48, B100**

~TYPES OF LIPOPROTEINS~

	type	density (g/ml)
Largest;	Chylomicrons	0.95
	Chylomicron remnants	1.0
	VLDL	1.0
	VLDL remnants	1.05
	LDL	1.1
Smallest	HDL	1.2

* *The higher the density, the greater the cholesterol content (cholesterol is the densest of the transported lipids)*
THUS the big chylomicrons are almost completely full of triglycerides
And HDL is made completely of cholesterol.

ingested TRIGLYCERIDES

→ **Pancreatic lipase**

Fatty Acids

@ Duodenal or jejunal epithelial cell

Reassembled and packaged into CHYLOMICRONS
Which are **too big** to travel through capillaries in the gut;
THUS: must use the lymphatics!
Very unusual; chylomycrons totally bypass the liver, so there is no first pass metabolism

Into circulation →
Via the Thoracic Duct

chylomicrons Immobilised @ capillary beds

Lipoprotein Lipase (LPL) @cell surface extracts the triglycerides and breaks them down to monoglycerides and FFAs

ApoC2 switches on LPL

Chylomicron remnants are slightly richer in cholesterol

Recirculate and get taken up by up by the liver which recognises ApoB48 and ApoE

~LIVER~

HDLs: the GOOD cholesterol
→ are the BACKWARD TRANSPORT of cholesterol esters to the liver;
EARLY HDL: no cholesterol; just a disk of lecithin; and ApoA1 is present in the coat: docks with cells which are releasing cholesterol.
→this causes uptake of cholesterol into the HDL blob; BUT: the cholesterol is immature,i.e needs to be esterified. This is done by the enzyme Lecithin Cholesterol Acyl-Transferase (LCAT) which transfers one fatty acid from lecithin into the cholesterol (thus esterifying it) and leaving a lysophosphatidyl-choline remnant (glycerol backbone with just one fatty acid);
THUS THE MATURE HDL IS FORGED

VLDLs get synthesised and released by the LIVER: used in starvation as a source of energy

LPL **ApoC2 switches on LPL**

VLDL remnants (slightly richer in cholesterol) are either reabsorbed by the liver, or modified in the circulation into **LDLs**

LDLs: only one **apoprotein (B100)**
→ bind to surfaces of cells which need cholesterol via LDL receptors
(statin drugs usefully promote experession of these)
!! if the apoB100 protein gets oxidised or glycosylated (eg. in diabetes) it can no longer be recognised by the LDL receptor: needs to be taken care of by the "scavenger" receptor of macrophages: and macrophages then turn into the FOAM CELLS of atheroma!!

The properties of the principal lipoprotein classes

Lipoprotein class	Major lipids	Apoproteins	Density (g/ml)	Diameter (mm)	Origin	Destination
Chylomicrons	TAG and SE from diet	A I , A II , **B 48** **C II** , C III , E	<0.94	80-500	Enterocytes	Capillary beds in adipose tissue
Chylomicron remnants	CE from diet	A I , A II , **B 48** C II , C III , **E**	<1.006	40-100	Capillary beds	Hepatocytes
VLDL	TAG from liver	**B 100** , C II C III , E	<1.006	30-80	Hepatocytes	Peripheral capillary beds
VLDL remnants	TAG and CE	**B 100** , C III , **E**	<1.019	25-35	VLDL	LDL
LDL	CE	**B 100**	1.019-1.063	15-25	VLDL	Peripheral tissues and hepatocytes
HDL	Cholesterol, CE and TAG	**A I , A II , E**	1.063-1.21	5-12	Enterocytes	Hepatocytes

Where an apoprotein has a demonstrated function with respect to a particular lipoprotein class, the code is shown in boldface. Only apoproteins discussed in the text have been included; others have been identified, but their functions have not yet been established unequivocally.

CE, cholesterol ester; TAG, triaclglycerol; VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins

Physiology of Blood Vessels

RULES OF THUMB:

Any substance which is the product of metabolic activity will lead to

VASODILATION, eg.

- **CO2**
- **Adenosine**
- **Lactic acid**

RULES OF THUMB:

SHEAR STRESS → VASODILATION (endothelium under stress will release a lot of Nitric Oxide (NO))

→ **hence VASODILATION**

in fact… NO (aka. EDRF, "Endothelium-derived Relaxation Factor") is THE vasodilator

→ many other vasodilators actually just cause NO release, such as

- **HISTAMINE,**
- **BRADYKININ,**
- **SUBSTANCE P,**
- **ACETYLCHOLINE**