Coronary Heart Disease

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Diana Gorog

About Us The National Heart and Lung Institute of Imperial College, based in South Kensington, London, is recognized for its excellence in cardiovascular research both nationally and internationally, in both basic science and translational research.

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Introduction

- Globally, cardiovascular disease (CVD) remains the leading cause of mortality and morbidity, despite many preventative and therapeutic advances. CVD accounted for some 18 million deaths worldwide in 2015, and this number is expected to grow to >23.6 million by 2030.
- The predominant cause of cardiovascular death is ischemic heart disease, for both men and women. Advancing age is the strongest risk factor.
- Global CVD rates rose by 12.5% between 2005 and 2015, with deaths attributable to ischemic heart disease (IHD) increasing by 16.6% to 8.9 million deaths. Over the same time period, age-standardized mortality rates for IHD fell by 12.8%, reflecting improved survival of patients.
- Recent data from the Office for National Statistics in 2015 show that in England and Wales, more people now die from dementia than heart disease, with dementia being the leading cause of death in women, although IHD continues to be the leading cause of death in men.
- There is, therefore, an important ongoing need to further reduce mortality and morbidity from IHD, and an appreciation of the pathophysiology of IHD is essential to enable this.

Pathophysiology

Atherosclerosis

Risk Factors for Development of Coronary Artery Disease

- Both genetic and environmental factors contribute to the development of coronary atherosclerosis. Genome-wide association studies have revealed more than 55 loci related to

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A. Myat et al. (eds.), *The Interventional Cardiology Training Manual*,
https://doi.org/10.1007/978-3-319-71635-0_1

coronary atherosclerosis, and it is mainly individuals with combinations of multiple variants who are at greatest risk.

- Several of the genes implicated encode proteins that relate to cardiovascular risk factors, such as lipids, lipoproteins, systemic inflammation, and hypertension. Some of the more recently identified loci encode genes with well-documented roles in vessel wall biology.
- ABO blood type impacts the risk of myocardial infarction. Individuals with blood type A or B are at greater risk of MI compared to individuals with blood type O.
- The demonstration of a genetic link between a mutation in the LDL-C receptor and development of premature coronary atherosclerosis culminated in the development of statins.
- The enzyme proprotein convertase subtilisin kexin 9 (PCSK9), located on chromosome 1p32.3, increases the degradation of LDL-C receptors. Mutations that increase the function of PCSK9 are associated with high levels of LDL-C and increase the incidence of coronary atherosclerosis. In contrast, mutations that result in loss of function of PCSK9 are associated with low levels of LDL-C and decrease the incidence of coronary atherosclerosis. These observations resulted in the development of monoclonal antibodies that inhibit the function of the PCSK9 enzyme and dramatically decrease LDL-C.
- Smoking impacts all phases of atherosclerosis from endothelial dysfunction to acute thrombotic cardiovascular events, particularly myocardial infarction. Both active and passive cigarette smoke, as well as air pollution, increases inflammation and thrombosis risk.
- Hypertension and diabetes mellitus (DM) are major risk factors contributing to the development of coronary atherosclerosis.
- Renal impairment, in particular end-stage renal disease, confers an excess cardiovascular risk, with a significant increase in the burden of coronary atherosclerosis and thrombosis risk, over and above that predicted by traditional risk factor models.
- A sedentary lifestyle may predispose to obesity and DM, which are associated with hyperlipidemia and an inflammatory process. Thus, moderate exercise and a balanced diet, particularly a Mediterranean diet, are recommended and have been shown to be associated with reduced cardiovascular risk.

Coronary Atherosclerosis

- Subclinical coronary atherosclerosis in the form of early intimal hyperplasia, usually near arterial branch points, may be apparent in infancy. Lesions can progress to pathological intimal thickening, which may be seen initially as "fatty streaks," namely subendothelial lipid deposits, even in adolescents.
- Atherosclerosis is considered to be the result of a complex, chronic inflammatory process. Coronary atheroma is classified in order of increasing severity in descriptive terminology as adaptive intimal thickening, intimal xanthoma (fatty streak), pathological intimal thickening, and fibroatheroma.
- Immune cell infiltration is most apparent in early atherosclerotic lesions, while uptake of monocytes and differentiation into macrophages, together with smooth muscle cell (SMC) infiltration and proliferation, accelerate atheroma progression (Fig. 1.1).
- Activation of inflammation can precipitate acute coronary syndromes (ACS) due to plaque rupture. The invasion of lipid pools by macrophages leads to foam cell formation and conversion of plaques into early and late fibroatheromas with large necrotic cores. Necrotic cores, arising from macrophage infiltration of lipid pools, further develop and expand, sometimes rapidly through intraplaque hemorrhage (IPH) from leaky vasa vasorum, principally from intimal microvessels originating within the adventitia, accompanied by free cholesterol derived from erythrocyte membranes and secondary macrophage response (Fig. 1.2).
- A fibrous cap separates the necrotic core from the vessel lumen and its structure and composition determine the potential for coronary thrombosis. Infiltrating macrophages and

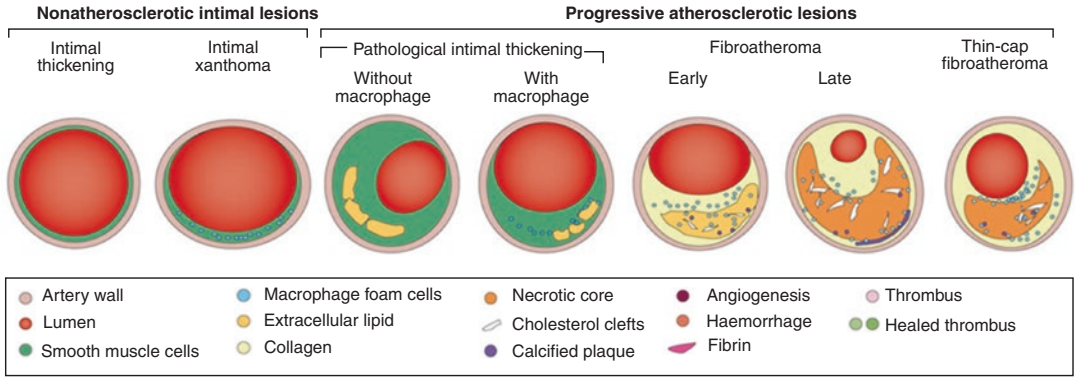

Fig. 1.1 Human coronary lesion morphologies categorized as nonatherosclerotic intimal lesions, progressive atherosclerotic lesions, lesions with acute thrombi, and complications of hemorrhage and/or thrombus with healing and stabilization. Yahagi, K. *et al.* (2015) Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nat. Rev. Cardiol.* https://doi.org/10.1038/nrcardio.2015.164

release of active proteases can result in thinning of the fibrous cap, which may lead to plaque rupture, the most frequent cause of acute coronary thrombosis. Not all thin caps eventually go on to rupture; mechanical stress is probably critical to this process.

- When an atherosclerotic plaque initially develops, the artery undergoes remodeling in which the luminal area of the artery may not be diminished. The degree of luminal stenosis, therefore, may not be directly related to the atherosclerotic plaque burden. Coronary calcification, often used as a screening test for coronary artery disease, is directly related to total plaque burden, but not to percent stenosis.
- Many high-grade stenosis may have little calcium content, particularly in younger individuals. Significantly more calcification is seen in stable than in unstable plaque, and with advancing age.

Progression of Coronary Atherosclerosis

- Morphological features of plaque progression include infiltration with macrophage foam cells, IPH, and reduction in fibrous cap thickness. However, plaque progression is not linear and advances through episodic rupture and healing.
- Atherosclerotic plaques can be stable or unstable. Unstable atherosclerotic plaques are characterized by a large lipid core, abundant macrophages, small amount of collagen, and a thin fibrous cap. In contrast, stable atherosclerotic plaques contain a small lipid pool, large amounts of collagen, few macrophages, and a thick fibrous cap.
- In a dynamic process, stable plaques at any time may become unstable, while an unstable plaque may be stabilized. Unstable plaques are prone to rupture, and this leads to initiation of intraluminal thrombosis, manifesting in ACS (Fig. 1.3).
- Subtotal or short-lived vessel occlusion may result in unstable angina or a non-ST-elevation MI (NSTEMI), while sudden complete occlusion without a supportive collateral circulation results in a ST-elevation MI (STEMI).
- While plaque rupture may manifest in ACS, more often it will be clinically silent, giving rise to repetitive cycles of nonocclusive thrombosis and healing. Organization of such nonocclusive thrombi with granulation tissue, with SMC infiltration and deposition of proteoglycans and collagen, converts this into a fibrous plaque, with repetitive cycles leading to progressive luminal narrowing.

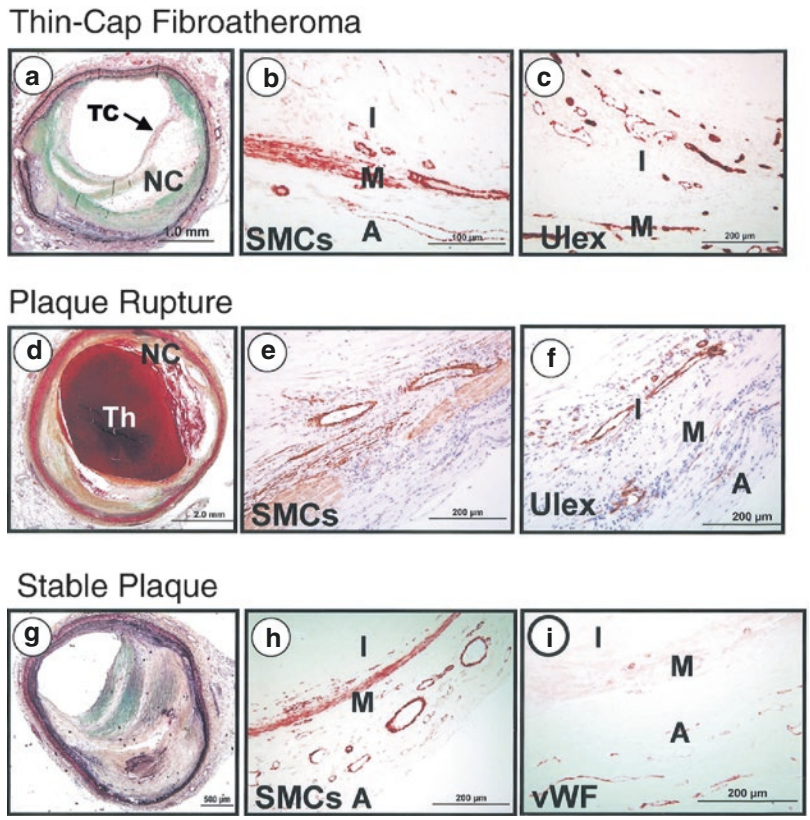

Fig. 1.2 Vasa vasorum in thin-cap fibroatheroma and plaque rupture compared with that in stable plaque in human.

Unstable atherosclerotic plaques thin-cap fibroatheroma (**a**–**c**) and rupture (**d**–**f**) are associated with marked neoangiogenesis. The microvessels close to the adventitial and medial layers (**b** and **e**) tend to be in contact with surrounding smooth muscle cells compared with intimal vessels closer to the lumen, which are characterized by a single lining of luminal endothelium (**c** and **f**). The main pathologic feature of the vulnerable plaque is an intact thin fibrous cap heavily infiltrated by macrophages (**a**). In plaque rupture (**d**), the fibrous cap is disrupted with a superimposed luminal thrombus. The adventitial vessels in unstable plaques often show perivascular smooth muscle cells (**b** and **e**). In contrast, the vasa vasorum close to the necrotic core is abnormal, consisting mostly of endothelial cells overlying a disrupted "leaky" basement membrane. (**g**–**i**) Stable plaques contain mostly collagen, proteoglycans, and calcium, and show fewer vasa vasorum in the intima, media, and adventitia. Endothelial markers: *Ulex europaeus* (Ulex) and anti-von Willebrand factor (vWF) antibody immunohistochemical staining; smooth muscle cell (SMC) marker: -actin. (**a**, **d**, and **g**) Movat pentachrome staining. *A* adventitia, *I* intima, *M* media, *NC* necrotic core, *TC* thin cap, *Th* thrombus. Jain RK, et al. Antiangiogenic therapy for normalization of atherosclerotic plaque vasculature: a potential strategy for plaque stabilization. Nat Clin Pract Cardiovasc Med. 2007;4:491–502. https://doi.org/10.1038/ncpcardio0979

Coronary Thrombosis

Vulnerable Plaque/Thin-Cap Fibroatheroma

- ACS is generally precipitated by a sudden increase in atherosclerotic lesion size with accumulation of erythrocytes and fibrin within the necrotic core, predominantly due to IPH, luminal thrombus, or plaque fissure.
- Postmortem studies revealed a frequent association between acute MI and rupture or erosion of a coronary atherosclerotic plaque, most often a thin-cap fibroatheroma (TCFA). Thus, the TCFA, the lesion most frequently associated with plaque rupture and coronary thrombosis, has been termed the "vulnerable plaque."
- Such plaques consist of a thin fibrous cap (<65 µm thick) overlying a large necrotic core.

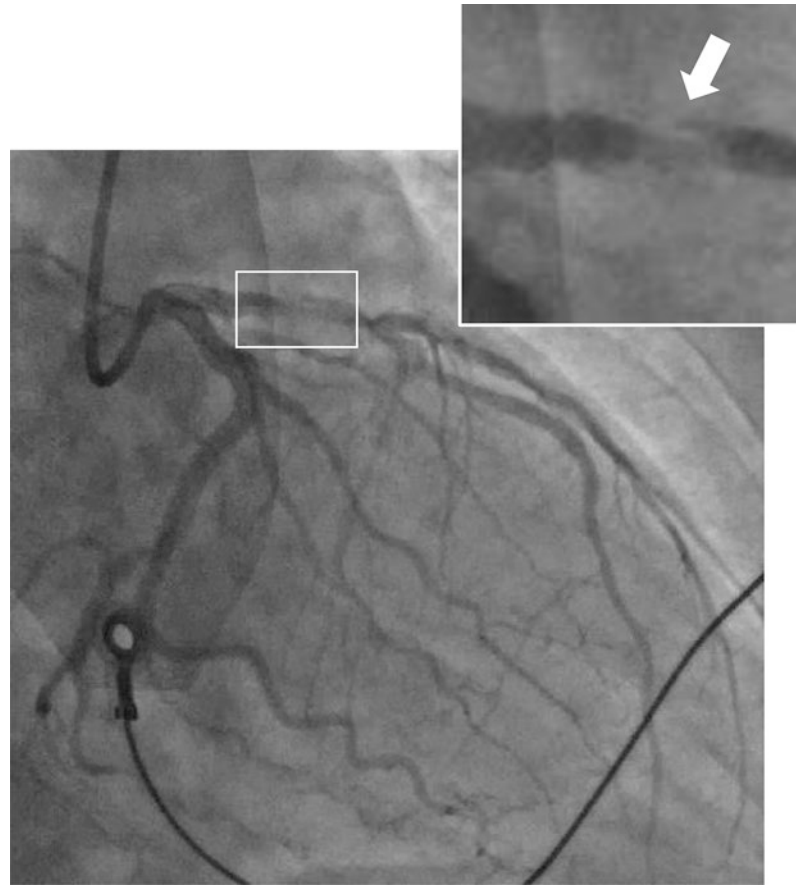

Fig. 1.3 Angiogram of left anterior descending coronary artery in a patient presenting with an acute coronary syndrome and anterior ST-segment depression, showing ulcerated plaque with rupture of the plaque shoulder in the proximal left anterior descending artery

The fibrous cap is composed predominantly of type 1 collagen with variable contents of macrophages and T-lymphocytes, and notable for the paucity or absence of SMCs.

- TCFA are more common in patients with high cholesterol, smokers, women aged >50 years, and patients with inflammation as evidenced by elevated hs-CRP.

Plaque rupture is the main mechanism responsible for coronary thrombosis. Rupture, usually affecting TCFA, occurs at the weakest point of the fibrous cap involving the shoulder regions of the plaque (Fig. 1.4). The intraluminal thrombus at the site of rupture, which may or may not be occlusive, is predominantly composed of platelets ("white thrombus'") (Fig. 1.5). The majority of plaque ruptures occur in vessels with >75% luminal narrowing.

Plaque erosion is responsible for some 25–30% of cases of coronary thrombosis, and occur usually on an underlying fibroatheroma, or less frequently on a background of underlying pathological intimal thickening. The intimal surface becomes denuded and luminal thrombi come into direct contact with a denuded intimal surface consisting of SMCs and a proteoglycan matrix. In the majority of erosions, the medial wall is intact and less inflamed than in ruptures. Additionally, in contrast to ruptures, which generally show positive remodeling, erosions involve negative remodeling. Such lesions are seen most frequently in women aged <50 years.

Calcified nodule is the least frequent cause of coronary thrombosis (<5%). It is a noted complication of highly calcified coronary arteries and more common in older patients. Calcified nodules typically occur in eccentric lesions, in areas

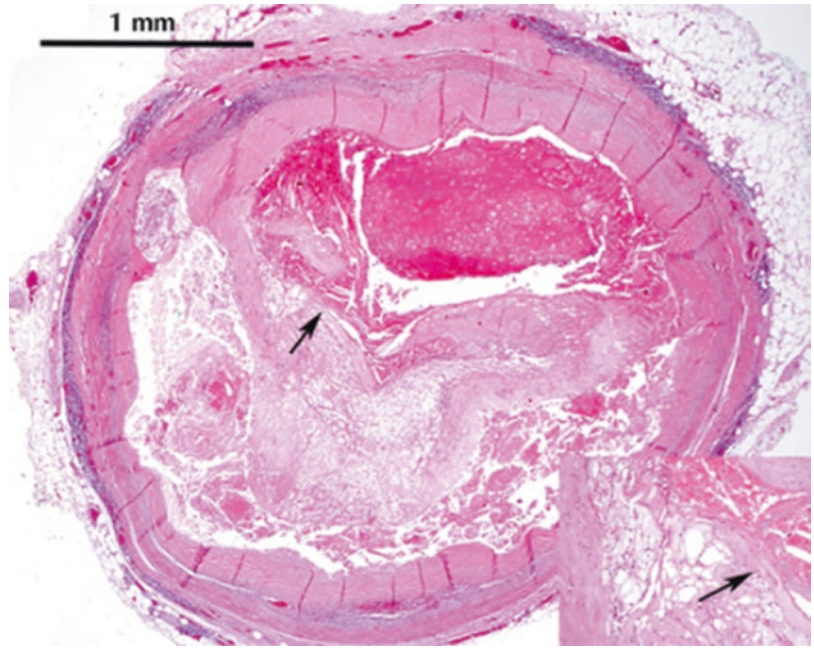

Fig. 1.4 Acute plaque rupture in the left anterior descending coronary artery. Low magnification showing acute occlusive thrombus overlying atheroma with rupture on shoulder (arrow, main figure, and inset) and communication of the thrombus with atheroma core. Hematoxylin and eosin, original magnification 20×. Tavora F et al. Frequency of acute plaque ruptures and thin cap atheromas at sites of maximal stenosis. Arq Bras Cardiol. 2010;94:143–9

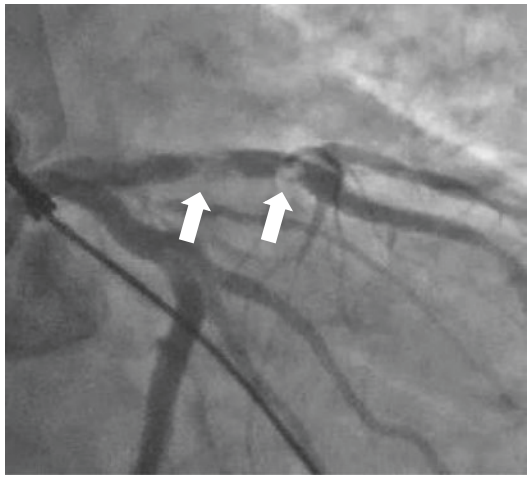

Fig. 1.5 Coronary angiogram showing filling defects representing thrombus in the left anterior descending coronary artery

of high torsion stress, where the protrusion causes disruption of the overlying luminal endothelium, which is likely to trigger platelet adherence.

Effect of Flow Dynamics

- At the pathologically high shear rates that exist in stenosed coronary arteries, thrombin and high shear stress play the most important roles in activation and aggregation of platelets leading to occlusive thrombus formation.
- The shear rates in severely stenosed arteries are determined by stenosis length, height, and plaque roughness. If shear rates exceed 10,000 s^{-1}, changes occur in the glycoprotein Ibα (GPIbα) receptors on the platelet surface and plasma von Willebrand factor (vWF) undergoes conformational transformation allowing creation of vWF-GPIbα adhesive bonds. This leads to the formation of aggregates downstream, in the post-stenotic segment where there is low shear (shear deceleration zone) and turbulent flow.
- Above shear rates of >10,000 s^{-1}, microvesicles are formed on the platelet surface, which are responsible for abundant thrombin generation.

Current View of ACS Causation

- Many vulnerable plaque ruptures are silent, without clinical sequelae, and frequently transition to *thick*-cap fibroatheromas or fibrotic plaques, leading to progressive luminal narrowing through repeated rupture and healing.

- In ACS patients, recurrent major adverse cardiovascular events occurring during follow-up are equally attributable to recurrence at the site of culprit lesions and to non-culprit lesions. Plaque ruptures are frequently observed in non-culprit lesions, indicating not only widespread vulnerability/inflammation, but also a "vulnerable patient" rather than a vulnerable plaque. It is probably for this reason that identifying individual lesions prone to rupture has not translated into ACS reduction.
- Most non-culprit lesions associated with recurrent events are angiographically mild at baseline (mean [±SD] diameter stenosis, 32.3 ± 20.6%), characterized by a large plaque burden of ≥70% or a minimal luminal area of ≤4.0 mm^2 or classified as TCFA on intravascular ultrasonography.
- ACS typically occur when an atherosclerotic plaque, usually TCFA, undergoes rupture or erosion, but for this to cause an ACS it needs to occur in association with a prothrombotic milieu.
- Coronary thrombosis is the result of an imbalance between prothrombotic drivers, namely enhanced platelet reactivity and activation of coagulation, and the natural defense system to prevent lasting thrombosis, namely endogenous thrombolysis.
- While many studies have shown markers of enhanced platelet reactivity and coagulation to predict thrombotic events, altering antiplatelet medication for an individual based on the results of platelet function tests has thus far not translated into a clinical benefit.
- Both prevention and treatment of ACS are aimed at stabilizing vulnerable plaques, as well as promoting a less prothrombotic milieu.

Terminology and Definitions

Ischemia/Reperfusion Injury

- It is well recognized that the deleterious effects of hypoxia (ischemia) during STEMI are attenuated by prompt restoration of blood flow (reperfusion), leading to reduction in myocardial infarct size. However, reperfusion could paradoxically induce and exacerbate tissue injury and necrosis.
- Reperfusion injury, first described in 1960 in a canine model, is the term used to describe detrimental effects associated with reestablishing the blood supply over and above that sustained during the preceding ischemic period.
- The endothelial layer of distal microvasculature is particularly susceptible to the deleterious consequences of ischemia and reperfusion (ischemia/reperfusion, IR). The mechanisms underlying this phenomenon are complex and multifactorial, including calcium overload, generation of reactive oxygen species, endoplasmic reticulum and mitochondrial dysfunction, activation of protein kinases, inflammation, endothelial dysfunction, and appearance of a prothrombogenic phenotype.
- The presence of coexisting cardiovascular risk factors and events occurring during fetal life (fetal programming) markedly enhances the susceptibility to IR. The response to IR is bimodal, depending on the length of IR. While prolonged episodes of ischemia, conventionally taken as >20 min, cause persistent deleterious downstream effects despite reperfusion, brief periods of IR may be cardioprotective (see below).
- The RISK pathway refers to a group of protein kinases that, when activated, attenuate reperfusion injury. In animal models, activation of the RISK pathway by pharmacological or mechanical interventions such as ischemic preconditioning or postconditioning can reduce infarct size by up to 50%.
- While pharmacological modulation of IR through activation of the RISK pathway by administration of atrial natriuretic peptide, protein kinase C-delta inhibitor, glucagon-like peptide 1, darbepoetin alfa and atorvastatin, or pharmacological inhibition of mitochondrial permeability transition pore opening with cyclosporine has shown initially encouraging results in small studies, these manoeuvres have not translated into tangible benefits in patients with STEMI.

Preconditioning, Postconditioning, and Remote Conditioning

- Brief exposure of the heart to short bouts of ischemia and reperfusion (IR) prior to prolonged reductions in coronary blood flow (index ischemia) exerts powerful infarct-sparing effects (ischemic preconditioning, IP). This cardioprotective mechanism has been demonstrated in other organs as well.
- Preconditioning exerts a biphasic effect, with an acute cardioprotective effect becoming apparent within minutes and lasting up to 2 h after the brief preconditioning ischemia and a second window of *delayed preconditioning* that becomes apparent 24–72 h after the initial insult.
- While the exact mechanisms are likely multifaceted and not fully understood, adenosine release appears to play a role in the initiation of acute preconditioning which is protein synthesis independent, while nitric oxide appears to play a major role in delayed preconditioning, effects that require protein synthesis.
- IP diminishes the effects of prolonged ischemia in animal models by reducing microvascular endothelial dysfunction, capillary plugging, leukocyte adhesion and emigration, and protein leakage.
- Cardioprotection can also be achieved by inflicting brief repetitive episodes of IR to an organ or a tissue remote from the heart; this is known as remote ischemic conditioning. Repetitive cycles of IR can be applied before the major (index) ischemic event (preconditioning), during the event (perconditioning), or shortly after reperfusion (postconditioning).
- Studies on perconditioning have applied remote ischemia in patients with STEMI either pre- or during PPCI, with mixed results, and further studies are ongoing.

Warm-Up Angina

- Warm-up angina refers to the attenuation or abolition of angina on a second period of exercise, when separated from the first period of exercise by a brief rest. It is evidenced by reduced symptoms of chest pain, reduced ST-segment depression, and reduced ischemic ventricular arrhythmias on the second compared to the first exercise. It has been likened to ischemic preconditioning; however, warm-up ischemia does not seem to be mediated by adenosine or by cardiac adenosine triphosphate-sensitive potassium channels.

Myocardial Stunning

- The ventricular contractile dysfunction that temporarily persists following a period of ischemia and after restoration of normal, or near-normal coronary flow, despite the absence of irreversible damage, is termed myocardial stunning.
- Such contractile dysfunction is relatively short-lived and followed by full functional recovery. It has been proposed that myocardial stunning appears to result from reperfusion and may be an adaptive response that affords protection against the effects of prolonged IR.
- Interventionalists and intensivists should be aware of this phenomenon, since it explains why assessment of myocardial function may not be reliable for some time after PPCI for STEMI, and why supportive measures with inotropic or mechanical support may need to be continued for some time after successful reperfusion before maximal ventricular functional recovery can be expected.

Myocardial Viability/Hibernation

- Myocardial hibernation describes an adaptive phenomenon observed in patients with coronary artery disease, where repeated episodes of ischemia lead to cumulative stunning, culminating in significant downgrading of myocardial contractility to better withstand reductions in oxygen and nutrient delivery, and prevent cardiomyocyte death.
- This adaptation involves reduction in myocyte contractility as well as a metabolic switch to use of carbohydrates as an energy source, to reduce energy demand.
- At a cellular level, characteristic changes include the appearance of polymorphic mitochondria, increase in lysosomes and reduction in myofibrils, as well as observation of

apoptosis and autophagy, regulating destruction of nonviable cells to enhance survival of hibernating ones.
- Hibernating myocardium demonstrates significant improvement in response to revascularization manoeuvres with PCI or CABG, with restoration of normal metabolism and contractile function. Assessment of myocardial viability, using echocardiographic, CMR, or nuclear perfusion modalities, is used to guide revascularization decision in patients with LV impairment.
- In patients with a similar extent of ventricular dysfunction, significant differences may exist in the relative extent of hibernation or scarring, which will impact the response to revascularization.

Special Circumstances

Saphenous Vein Graft Disease

- While native coronary atherosclerosis develops over decades, saphenous vein grafts (SVG) demonstrate accelerated atherosclerosis within months to years of surgery.
- Cardiovascular risk factors, including hypertension and cholesterol, predispose to SVG disease. Other predictors of SVG failure include graft diameter, target vessel characteristics, and grafting onto the right coronary artery.
- Vein graft attrition rate is 2% per annum from the 1st to the 7th postoperative years, increasing to 5% per annum from the 7th to the 12th years; at 10 years, only 38–45% of SVGs remain patent.
- Typical SVG atherosclerosis is concentric and diffuse, low in calcium content, and heavily lipid laden, with a thin fibrous cap (Fig. 1.6).
- The extensive lipid core is attributable to macrophage foam cell infiltration, resulting in apoptosis and formation of necrotic cores within 2–5 years after surgery. Subsequently IPH contributes to expansion of the necrotic core. Plaque rupture is observed between 5 and 10 years after surgery.
- SVG plaque is highly "friable" and prone to distal embolization. This can manifest in no reflow phenomenon and periprocedural MI in up to 15% of cases during PCI, mandating distal embolic protection where technically feasible.
- Accelerated atherosclerosis also affects SVG stents.
- High-dose statin therapy significantly reduces SVG atherosclerosis, but whilst antiplatelet therapy has been shown to reduce thrombosis-induced graft failure, it has not improved long-term patency.

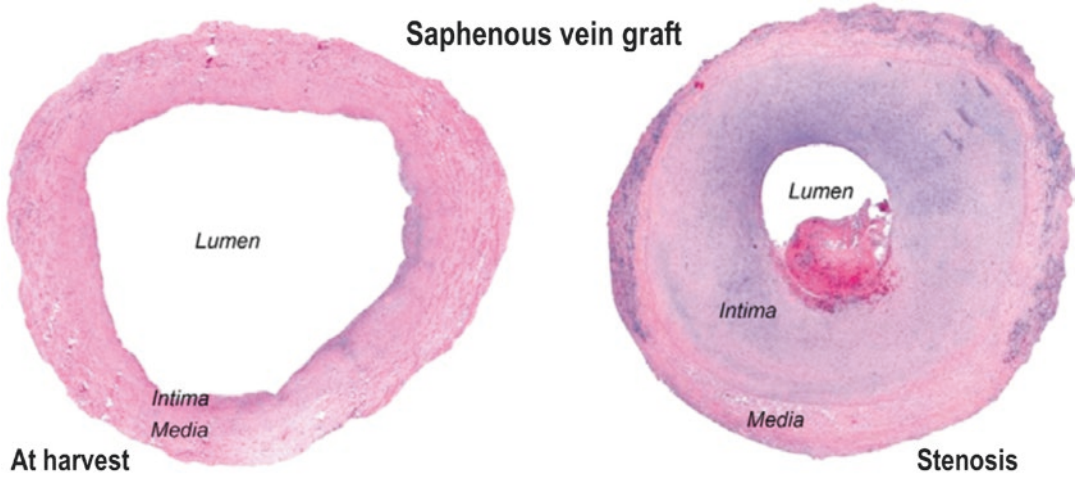

Fig. 1.6 Histology of saphenous vein graft cross section, showing concentric diffuse atherosclerosis with prominent neointima and remodeled media, causing significant stenosis. Garbey M, Berceli SA. A dynamical system that describes vein graft adaptation and failure. J Theor Biol. 2013;336:209–20

In-Stent Restenosis

- In-stent restenosis (ISR) is seen in 20–40% of bare metal stent (BMS) implantation. Early randomized controlled trials using drug-eluting stents (DES) showed ISR <6%, and subsequent real-world registries including longer and more complex lesions and patient subsets have shown this to occur in up to 20% of cases.
- ISR is the result of accelerated atherosclerosis, similar to that occurring in SVG. Whilst with BMS neointimal hyperplasia with smooth muscle cell hypertrophy characterizes ISR, with DES neoatherosclerosis is also very frequently seen.
- In-stent atherosclerosis or "neoatherosclerosis" is typified by macrophage foam cell infiltration. Such lipid-laden foam cells undergo apoptosis, resulting in the creation of necrotic cores. Necrotic cores of neoatherosclerosis do not communicate with the underlying native plaque.
- ISR is associated with neointimal calcification, with both BMS and DES, although it is more common with DES.
- Risk factors for ISR include procedural variables (including stent under-expansion, stent fracture, drug resistance, and hypersensitivity reactions), lesion characteristics (long lesions, bifurcations, small vessels, calcified or ostial lesions), as well as patient factors (age, diabetes, hyperlipidemia). The predominant pattern of angiographic restenosis with DES is focal (≤10 mm in length) in 70–80% of cases, whereas with BMS only <45% were focal and the rest diffuse.
- Whilst ISR occurs on average 5 months post-implant with BMS, it occurs later with DES up to 12 months.

Current Concepts and Future Directions

Despite significant advances in the understanding of complex atherosclerotic plaque morphology and alterations in plaque morphology associated with acute coronary thrombotic events, the recognition that plaque rupture occurs frequently without clinical sequelae has led to the realization that it is not an individual vulnerable plaque, but the co-occurrence of adverse alterations in plaque morphology in concert with a prothrombotic milieu that results in acute coronary thrombosis.

Thus future studies must look to both identify and favorably modulate not only local but also more widespread coronary and systemic atherosclerosis, as well as identify patients who are prothrombotic, with appropriate tailoring of antithrombotic and antiplatelet medications to those at risk.

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