Atherosclerotic Heart Disease

Massimo Slavich and Juan Carlos Kaski

Introduction to Atherosclerotic Heart Disease

Coronary Artery Disease

Coronary atherosclerosis, also termed coronary artery disease (CAD), is the most common type of heart disease and the most frequent cause of acute myocardial infarction. CAD accounts for approximately 15 % of all deaths in the developed nations. Despite the high prevalence (approximately 20 % in people over 60 years of age), a relevant reduction of CAD mortality has been seen in the last decades due to coronary reperfusion strategies, advances in antianginal medical therapy, heart failure treatment, and better control of cardiovascular risk factors.

CAD is a chronic inflammatory disorder characterized by focal lipid deposition within the arterial wall, which leads to the formation of atheromatous plaques that can reduce the coronary lumen and the blood supply to the myocardium (myocardial ischemia). CAD progression can lead to ischemic cardiomyopathy, a condition involving ischemic chronic left ventricular (LV) dysfunction and remodeling [1].

For its function, myocardium requires a continuous supply of oxygen via the coronary tree (see chapter "Overview" under part "Heart"). In subjects with healthy coronary arteries, blood flow increases as appropriate to match increased myocardial metabolic demand (coronary blood flow reserve). When an atherosclerotic lesion is present that affects blood flow, ischemia develops, as oxygen delivery cannot match myocardial requirements. This mechanism is often present in chronic stable angina pectoris (CSA), which usually manifests itself with exertional chest pain that is relieved by rest and/or with the administration of sublingual nitroglycerin, a nitric oxide (NO) donor [2]. This is different from acute myocardial infarction, which occurs when a coronary artery is acutely and unexpectedly occluded due to coronary thrombosis and/or epicardial coronary artery spasm. Under these circumstances, if the patency of the coronary is not restored promptly, necrosis of cardiac myocytes (CMs) ensues.

In the presence of reduced oxygen delivery, maladaptive metabolic changes occur within the myocardial cells.

This chapter discusses the mechanisms and major pathways of atheromatous plaque formation and myocardial ischemic conditions, mainly CSA.

Atherosclerotic Plaque Formation and Myocardial Metabolic Changes

Atheromatous plaque initiation and growth involve oxidized low-density lipoprotein (LDL), cholesterol deposition, endothelial activation and dysfunction, and inflammatory cell (i.e., macrophages

M. Slavich • J.C. Kaski (✉)
Cardiovascular Sciences Research Centre,
St George's University of London,
Cranmer Terrace, London SW17 0RE, UK
e-mail: massimo.slavich@gmail.com;
jkaski@sgul.ac.uk

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and lymphocytes) activation [1]. Elevated concentrations of circulating LDL cholesterol facilitate subendothelial ApoB lipoprotein retention especially in arterial sites showing turbulent flow. Once in the arterial intima, LDL particles undergo oxidation (e.g., by reactive oxygen species). Debris and cholesterol crystals accumulate in the vessel wall, associated with accumulation of different leukocytes. Lipid peroxidation in the plaque enhances the expression of adhesion molecules that can in turn contribute to intimal leukocyte recruitment. Subsequent structural modifications progressively weaken the arterial wall.

Within the atheromatous plaque, several pro- and anti-inflammatory cytokines and chemokines contribute to lesion growth, e.g., migration inhibitory factor and type 1 interferons, are typically overexpressed and exert proinflammatory and proatherogenic functions. Increased amounts of chemotactic chemokines recruit leukocytes and mediate transendothelial diapedesis.

Within these initial lesions, known as "fatty streaks," recruited monocytes differentiate into macrophages, which ingest LDL. These lipid-laden monocytes turn into foam cells. Subsequently, a necrotic core forms, surrounded by a fibrous cap composed of collagen and smooth muscle cells. Neutrophils and dendritic cells (DCs) are also involved in the progression of the atheroma. DCs take up lipids and further accumulate in clusters with T cells in the so-called high-risk rupture plaque region. In this region, T cells account for almost 20 % of the cells in the plaque. Their proinflammatory status further enhances leukocyte recruitment and activation. Local inflammatory processes lead to the degradation of the collagen in the fibrous cap and the extracellular matrix weakening the fibrous cap and compromise plaque stability. A thin fibrous cap and continuous accumulation of lipids can create a "high-risk" or "vulnerable" plaque. Through the release of metalloproteinases, macrophages have a pivotal role in plaque rupture [1, 3].

Myocardial Ischemia and Heart Metabolism

Heart metabolism critically relies on the production of sufficient ATP to allow muscle contraction and Ca^{2+} cycling. The intracellular Ca^{2+} levels are strictly controlled and their increase, subsequent to metabolic dysfunction, leads to impaired CM contractility (Fig. 1) [4].

Under physiological conditions, free fatty acids (FFA) are the main source of energy, which is more efficient than carbohydrate oxidation, albeit at the expense of greater oxygen consumption (see chapter "Overview" under part "Heart"). A rapid increase in workload induces a shift from FFA to glucose oxidation (metabolic switch). During myocardial ischemia, diminished perfusion leads to inadequate oxygen delivery that compromises oxidative phosphorylation and therefore ATP generation. The diminished ATP levels induce the loss of contractile force and reduce the activity of ATP-dependent ion transporters (Fig. 1). Even under hypoxic conditions, the myocardium continues to derive a large proportion of its energy from FFA oxidation. However, in order to supply more ATP, glycolysis increases, prevailing over FFA oxidation. This leads to further metabolic changes, including intracellular acidosis, modified signaling, increased saturated FFA oxidation, and possibly apoptosis [5].

After a severe ischemic event, CMs can remain viable in the form of "stunned myocardium" which describes a prolonged but reversible LV dysfunction that initially persists despite the restoration of blood flow to the affected area. "Myocardial hibernation," another form of myocardial oxygen deprivation and reduced ventricular function, develops in response to a chronic and substantial reduction of coronary blood supply; in both hibernating and stunned myocardium, cells are still alive but do not have enough energy to contract.

In the short term, a reduced contractile response to Ca^{2+} is present during hibernation. During prolonged hibernation, fetal genes are reactivated resulting in a switch from fat to glucose metabolism [6, 7]. On restoring artery patency, FFA oxidation becomes active again, prevailing over glucose oxidation.

Revascularization may improve or restore the functional capacity in the hibernated area. Although the restoration of blood flow to ischemic myocardium is beneficial, on occasions, it can lead to further cell damage, i.e., "myocardial reperfusion injury" [8]. This is characterized by

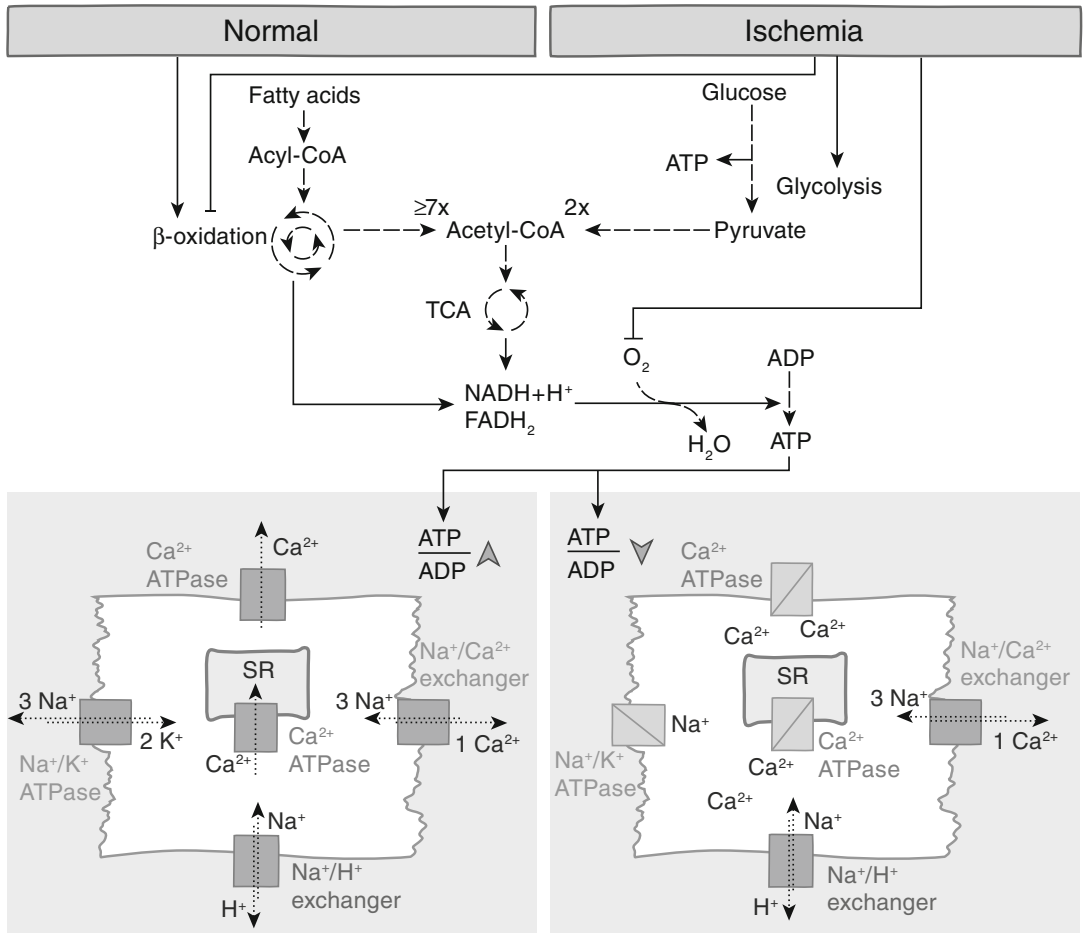

Fig. 1 Metabolic changes during myocardial ischemia. *Upper part*: Whereas fatty acid (FA) oxidation via β-oxidation is the preferred source of energy under normal oxygen supply, under hypoxic conditions (ischemia), energy metabolism switches to glucose oxidation, which requires less oxygen but also yields less ATP. Ischemia acts by reducing β-oxidation, increasing glycolysis, and limiting the supply of O_2 for oxidative phosphorylation. TCA, tricarboxylic acid cycle (also called citric acid cycle). *Lower part*: During ischemia, ATPase function is impaired as the ATP/ADP ratio is decreased. This leads to an intracellular Ca^{2+} and Na^+ overload, as Na^+/H^+ exchanger and Na^+/Ca^{2+} exchanger remain active, whereas Na^+/K^+-ATPase and Ca^{2+}-ATPase are dysfunctional. The resulting increase in Ca^{2+} further impairs myocardial function. *SR* sarcoplasmic reticulum

Ca^{2+} overload and the release of cytotoxic reactive oxygen species induced by the sudden restoration of blood flow [8].

Antianginal Treatment and Influence of Treatment on Cardiac Metabolism

First, appropriate management of modifiable risk factors, i.e., obesity (see chapter "Metabolic syndrome"), smoking, dyslipidemia (see chapter "Hyperlipidemia"), hypertension (see chapter "Hypertension"), and diabetes mellitus (see chapter "Diabetes mellitus"), reduces ischemic events and long-term cardiovascular risk. A healthy lifestyle, reduced oxidative stress, inflammation, and improved cardiac metabolism represent useful measures to reduce cardiovascular risk.

Pharmacological agents available at present act by reducing oxygen demand, increasing coronary blood flow, or affecting myocardial metabolism directly. Although medical treatment in CSA patients often provides effective control of symptoms [9], some patients require

percutaneous coronary intervention (PCI), in which a balloon is inflated within the occluded artery to improve coronary blood flow and prevent recurrent ischemia [2]. Especially in acute ischemia, rapid restoration of coronary blood flow to the affected area with PCI results in reduced mortality.

Obstructive stenoses that reduce blood flow and cause symptoms can be effectively treated with bypass surgery or PCI and stenting. Deploying a stent restores coronary blood flow and results in symptom improvement.

Pharmacological Treatment of Angina Pectoris

Current pharmacological CAD treatment aims to (i) abolish or reduce symptoms and improve quality of life, (ii) prevent ischemic episodes, (iii) reduce CAD progression and the risk of acute coronary events, and (iv) improve survival. Pharmacological antianginals act by reducing myocardial oxygen demand and/or improving blood supply via peripheral and coronary vasodilation and reduction of blood pressure and heart rate. While for many years the treatment of CAD has been based on agents acting on hemodynamic mechanisms, pharmacological agents are now available that beneficially affect the metabolic response of the ischemic heart and represent a useful alternative or adjunct to conventional antianginal agents [5]. Finally, agents that improve endothelial function are also useful.

Identifying the prevailing mechanism responsible for the development of myocardial ischemia is useful to design rational therapeutic strategies to reduce symptoms and prevent ischemic episodes. In patients with angina triggered by coronary artery spasm leading to a primary reduction of O_2 supply, vasodilators are the first-line therapy. In patients with obstructive CAD, drugs that reduce heart rate and blood pressure, such as β-blockers and calcium channel blockers (CA), are desirable. Negative chronotropic agents are especially useful, as heart rate is a major determinant of energy expenditure and prognosis [10]. In developed CSA, different therapeutic options are required to protect and rescue damaged myocardium. Nitrates improve oxygen supply (by vasodilating activity) and reduce myocardial metabolic demand (by reducing ventricular pre- and afterload). Diuretics and angiotensin converting enzyme inhibitors (see chapter "Hypertension") are commonly used in order to reduce the ventricular loading, especially in patients with advanced CAD and systolic dysfunction.

CAs act as vasodilators by preventing effective constriction of smooth muscle cells and reducing the heart rate (negative chronotropic effect). Non-dihydropyridine CAs have negative inotropic effects, reducing heart contractility, as higher level of Ca^{2+} in CMs is required for effective contraction.

β-Blockers act on multiple levels to improve disease progression and outcome, by blocking β-adrenergic receptors. They show negative inotropic and chronotropic effects, acting on the heart directly providing a reduction of oxygen demand and preventing transient myocardial ischemia. Some classes (carvedilol) additionally have a direct metabolic effect, inducing a metabolic shift to glucose utilization, reducing FFA uptake [11]. Finally, they enhance the bioavailability of NO, inducing vasodilation [12].

Ivabradine is a novel drug, which only lowers the heart rate (negative chronotropic), without interfering with the inotropism, because of its selective inhibition of the funny current (a mixed sodium-potassium current) in the cardiac pacemaker myocytes [13]. On the other side, drugs as dopamine and epinephrine are able to increase the inotropism and the chronotropism and are effective especially in advanced CAD and in patients with severely impaired LV function.

Trimetazidine and ranolazine directly modulate CM metabolism and thus reduce heart energy demand and loading conditions of the LV. This modifies neurohormonal activation and delays the occurrence of cardiac remodeling (see chapter "Heart failure" and Fig. 2). They have no direct effects on blood pressure or heart rate and are used as adjunctive therapy.

Trimetazidine inhibits the action of 3-ketoacyl coenzyme A thiolase, an enzyme implicated in the β-oxidation [14]. The resulting switch from FFA to

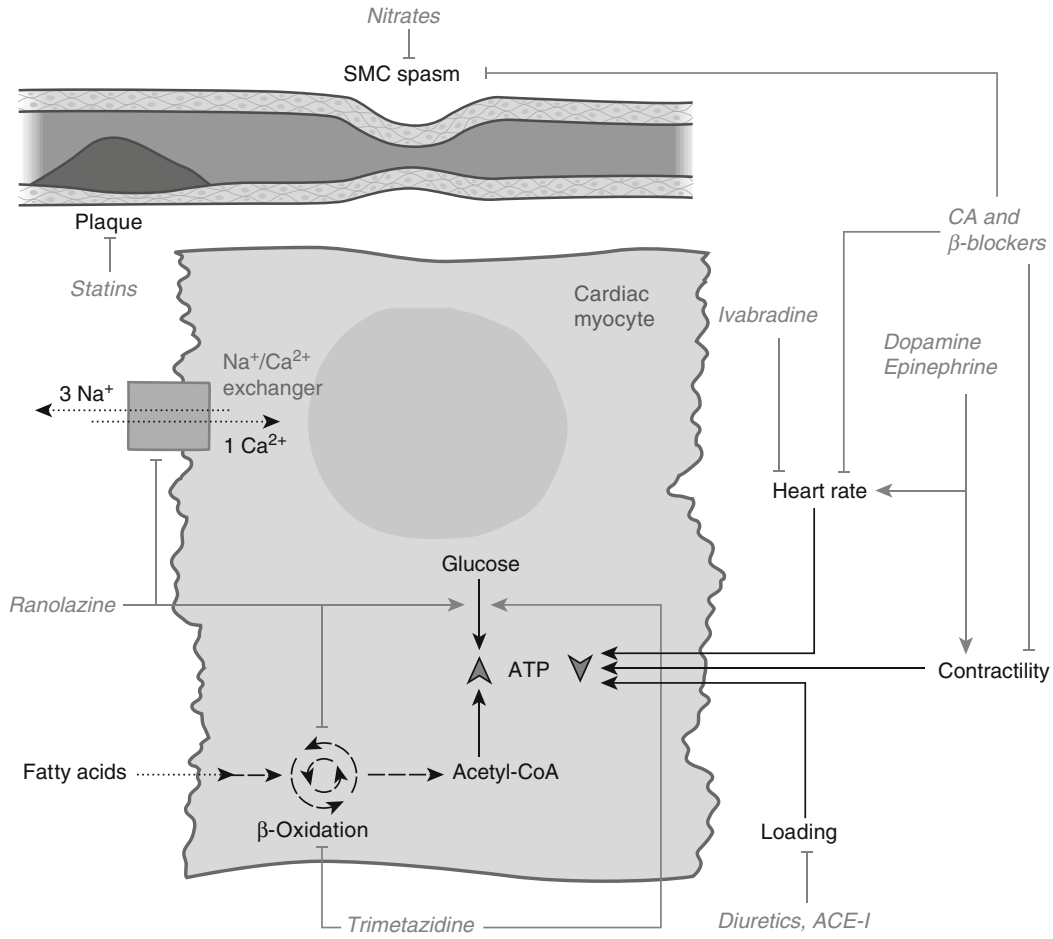

Fig. 2 Effects of treatment on cardiac metabolism. Statins interfere with atheromatous plaque formation in blood vessels by reducing the available cholesterol. Nitrates stimulate vasodilation via a nitric oxide (NO)-dependent effect on smooth muscle cells, increasing the blood supply to the cardiac myocytes (CMs). Ca^{2+} channel antagonists (*CA*) are effective in the regulation of spasm control, acting on vascular smooth muscle cells. Heart rate can be decreased (by CAs, β-blockers, and ivabradine) to prevent excessive strain (negative chronotropy) and can be increased (by dopamine and epinephrine) to prevent life-threatening reductions in contractility in late-stage and severe coronary artery disease (positive chronotropy). Cardiac contractility can be increased by dopamine and epinephrine and depressed by CA and β-blockers (positive and negative inotropy, respectively). Enhanced cardiac activity (heart rate, inotropism) requires a lot of ATP and thus oxygen. Diuretics and angiotensin converting enzyme inhibitor (*ACE-I*) reduce ventricular loading. Ranolazine and trimetazidine directly act on the metabolic pathway of the CMs, by favoring glucose oxidation and inhibiting β-oxidation. Ranolazine also reduces Ca^{2+} overload at the level of the Na^+/Ca^{2+} exchanger

glucose oxidation optimizes cellular energy processes and enhances ATP production during ischemia, as glycolysis requires less oxygen [15]. In this way, trimetazidine ensures the proper functionality of ion pumps, prevents CM apoptosis, and limits myocardial reperfusion injury [16], improving the LV function and long-term survival [17].

Ranolazine is a partial FFA oxidation inhibitor and shifts ATP production from FFA to glucose oxidation. Moreover, it prevents calcium overload during myocardial ischemia by inhibiting the Na^+/Ca^{2+} exchanger. In CAD patients, the addition of ranolazine to standard therapy decreases angina recurrences and increases exercise tolerance [18].

In order to interfere with the plaque formation and progression, achieving normal cholesterol levels is recommended. Statins inhibit

hydroxymethylglutaryl-CoA reductase, a key enzyme in cholesterol synthesis (see chapter "Hyperlipidemia"), lowering the circulating cholesterol level thus acting on or preventing atherosclerotic lesions [19]. Since atherosclerotic plaque disruption exposes the procoagulant endothelial layer, antiplatelet agents are also adopted in order to prevent thrombus formation.

Perspectives

Treatment of CAD aims to improve the patient's life quality and to reduce serious cardiovascular events that may lead to death or further morbidity. Despite the significant reduction in CAD mortality and morbidity in recent years, several issues still need to be addressed, i.e., mechanisms of atherosclerotic plaque progression, the early identification of atheromatous plaques prone to rupture, and the rational management of the different forms of ischemic heart disease.

Early reperfusion strategies in myocardial infarction have also resulted in a significant reduction of infarct size and mortality, but many issues still remain unsolved, including how to minimize reperfusion injury after acute coronary revascularization.

CSA affects a large proportion of individuals worldwide and its pharmacological treatment, albeit effective in a large proportion of cases, is far from ideal. The advent of newer antianginal drugs that directly affect metabolic pathways in the myocardium has opened new avenues for CAD management. Notably, technical advances in the field of coronary revascularization with new generations of biodegradable stents [20] are expected to result in improved patient management and less in-stent restenosis.

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