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1. PATHOPHYSIOLOGY AND CLASSIFICATION OF CARDIOVASCULAR DISEASES CAUSED BY ATHEROSCLEROSIS

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Cardiovascular diseases are the leading cause of mortality in the developed world and are becoming more and more important as the cause of mortality in the developing counties as well. Most of them are caused by atherosclerosis.

The terms atherosclerosis and atheroma are derived from Greek words athera meaning gruel, skleros meaning hard and oma meaning a mass. They accurately describe the nature of advanced lesions which characterize this degenerative and inflammatory disease of the arteries.

The past decade has witnessed enormous progress in our understanding of the pathophysiological nature of atherosclerosis which begins with endothelial dysfunction, the trigger for which are risk factors such as hypercholesterolemia, smoking, hypertension, hyperhomocysteinemia, impaired glucose metabolism and possibly infectious agents such as Cytomegalovirus, Helicobacter pylori and especially Chlamydia pneumoniae. Particularly important is increased concentration of plasma low-density lipoproteins (LDL) rich in cholesterol, and oxidant stress since they play a major role in impairing endothelial function. They achieve this by activating proinflammatory signalling pathways such as nuclear factor kappa B (NFkB) and by reducing the bioavailability of nitric oxide (NO). Biomechanical forces on the endothelium caused by hypertension including low shear stress from disturbed blood flow also activate the endothelium. Hypertension also increases the formation of hydrogen peroxide and free radicals such as the superoxide anion and hydroxyl radicals in plasma and these substances reduce the formation of NO by the endothelium and increase leukocyte adhesion.

NFkB signal transduction pathway is an important regulator of the transcription of a number of proinflammatory genes, including those that lead to the expression of adhesion molecules, e.g. vascular cell adhesion molecule-1 VCAM-1, ICAM-1, and selectins. High-density lipoproteins (HDL) and the cholesterol they contain are, however, a protective factor for atherosclerosis, and have opposing effects on the endothelium. HDL prevents endothelial vasomotor dysfunction and reduces the expression of adhesion molecules. In response to lipoprotein oxidation, monocytes and lymphocytes are recruited to the artery wall. This involves the expression of adhesion molecules, chemotactic proteins, and growth factors for monocyte–macrophages. After subsequently penetrating beneath the endothelium, monocytes, transformed into macrophages, accumulate oxidized lipoproteins and turn into foam cells. This process is mediated by cell-surface receptors that recognize oxidatively modified LDL. Foam cells are the hallmark of early atherosclerosis. The collections of foam cells together with T lymphocytes on vessel surface could be visible to the naked eye as fatty streaks - flat yellow-gray areas.

Undamaged endothelium has an established capacity to prevent platelets aggregating into microthrombi and to regulate lipid entry into vessel walls. However, once damaged, its capacities in these respects are reduced, so aggregation of platelets occurs. Aggregation of platelets leads to release of platelet-derived growth factor (PDGF) which stimulates the migration and proliferation of smooth muscle cells (SMC). Macrophages and endothelium, as well as T lymphocytes, also release growth factors and cytokines (eg. PDGF, TGF–beta etc.) and are also responsible for migration of SMC from the arterial media into the intima. This migration is followed by intense proliferation of SMC with loss of their normal contractile function and an increase in synthetic function. Increased lipid uptake occurs simultaneously with an increase in SMC number, so that formation of foam cells from SMC is also common. SMC start to synthesize and secrete collagens, elastin and complex proteoglycans thus transforming a lipid lesion into a fibro-lipid atheromatous plaque. Fibroblast proliferation, which is also enhancend under these circumstances, leads to the synthesis and secretion of collagens, and related macromolecules as well, participating therefore in the genesis of the plaque.

Fibro-lipid plaque is the characteristic lesion of advanced atherosclerosis. It consists of a cap of fibrous tissue and SMC which confer mechanical stability of the plaque and separate the lipid rich thrombogenic core from the vessel lumen and circulating blood. The plaques expand at their shoulders by means of continued leukocyte adhesion and entry caused by the same factors as those mentioned earlier. Influx of leukocytes and activation of macrophages at the plaque shoulders which then release metalloproteases and other proteolytic enzymes causes fibrous cap fissuring. Recurrent fissuring of plaques with thin caps and large lipid-rich cores causes a step-wise increase in plaque size, with platelet aggregation at these spots, resealing of plaques, and partial incorporation of thrombus within complicated lesions. This transient non-occlusive thrombus formation in coronary arteries usually

presents clinically as unstable angina pectoris. However, deep ruptures resulting in occlusive thrombus formation in coronary arteries are the usual cause of acute myocardial infarction.

Whether a plaque will remain intact and therefore stable, or rupture and lead to occlusive thrombus formation in a coronary artery causing an acute coronary syndrome due to ischemia, depends upon a number of factors, the most important of which is its composition. Stable plaques have a thick fibrous cap, a small lipid core, and few inflammatory cells. In contrast, unstable vulnerable plaques have high lipid content, numerous inflammatory cells, and a thin fibrous cap containing reduced collagen and vascular SMC. Although unstable plaques are believed to account for only a small number of all atheromata in coronary arteries, they are responsible for most acute coronary events.

Anyhow, atherosclerosis of coronary arteries causes several major clinical categories largely determined by clinical history, physical examination and laboratory findings. These major clinical categories include angina pectoris (stable angina, unstable angina, silent ischemia, syndrome X, and Prinzmetal's variant angina), myocardial infarction (MI), ischaemic cardiomyopathy and sudden cardiac death due to coronary heart disease (CHD). Unstable angina pectoris and MI together with sudden ischaemic death are the mean features of so-called acute coronary syndrome.

Angina pectoris is a clinical syndrome caused by the delivery of insufficient oxygen to the heart muscle via the coronary arteries, leading to ischemia. Angina is characterized by episodic chest (precordial) discomfort, pressure or pain lasting up to 15 minutes. It is typically precipitated by exertion or strong emotions and relieved by rest or sublingual nitroglycerin. An angina attack may be precipitated by the first contact with cold air on leaving a warm room during cold weather. In unstable angina, as compared with stable angina, the chest pain is generally more intense, lasts longer, is brought on by less effort or even occurs spontaneously at rest (e.g. when the patient is sedentary); it is progressive in nature, or involves any combination of these changes. Unstable angina is caused by an acute but reversible increase in coronary obstruction due to rupture or fissuring of the fibrous cap of the atheromatous plaque with consequent thrombus formation.

Silent ischemia is myocardial ischemia detected on ambulatory ECG monitoring (characterized by transient ST segment depression of at least one mm. persisting for at least one minute) or during exercise stress testing, echocardiography or nuclear stress scintigraphy in the absence of chest pain or any other symptoms. It may be categorized into 3 types: type 1 patients are totally asymptomatic, type 2 are those who are symptomatic after a prior documented MI and type 3 patients who manifest silent ischemia but also may have symptomatic ischemia. At least 75% of the ischemia occurring in patients with stable angina is clinically silent.

Syndrome X is angina, or angina - like chest pain relieved by rest or sublingual nitroglycerin in patients who have an abnormal ECG in exercise test and myocardial lactate production during ischemia but no coronary atherosclerotic lesion proved on coronary angiography. The exact aetiology of this syndrome is unclear but most likely it represents a heterogeneous group of changes best characterized by a reduced capacity of the coronary circulation to augment blood flow in the face of an increase in oxygen demand.

Prinzmental's (or variant) angina is angina caused by a spasm occurring within 1 cm. of an obstruction of the proximal portion of a major coronary artery. It is characterized by chest discomfort at rest which is relieved after sublingual nitroglycerin and by ST segment elevation in ECG during the attack. However, between anginal attacks, which tend to occur with regularity at certain times of the day, the ECG may be normal. The changes are usually confined to a single epicardial coronary artery, but multivessel spasm can also occur as well as the spasm at different levels within the same vessel.

Acute myocardial infarction is ischaemic necrosis of the myocardium usually resulting from an occlusion by an acute thrombus of a coronary artery that supplies the damaged area, often after an atheromatous plaque rupture. The patients suffer from a deep chest pain or pressure often with radiation to the left arm or jaw which is similar to the discomfort of angina pectoris. However it is usually more severe, long-lasting, and is not relieved by rest or sublingual nitroglycerin. Some patients, particularly women, can have silent MI or only atypical chest discomfort. MI is also characterized by ECG changes: the classic presentation includes ST segment elevation, inversion of T waves and development of pathological Q waves or loss of R waves. The diagnosis of MI is aided by laboratory tests including increased creatine kinase activity, particularly MB izoenzime, and increased troponin and myosin.

Ischaemic cardiomyopathy is predominantly caused by diffuse coronary artery atherosclerotic disease. It is caused by chronic coronary artery stenosis myocardial fibrosis with diffuse loss of myocytes and results in impaired ventricular systolic function reflected by low ejection fraction (EF). The main symptoms of this chronic disease are effort dyspnoea and fatigue.

Sudden cardiac death is witnessed death that occurs suddenly, i.e. within one hour of the onset of symptoms in an apparently healthy person, where death could not be ascribed to other causes. The main reason is cardiac arrest, i.e. absent or inadequate ventricular contractions that immediately result in systemic circulatory failure. It results primarily from electrical dysfunction, particularly ventricular fibrillation, asystole or electromechanical dissociation very often caused by MI. However it is not only atherosclerosis of the coronary arteries that is important.

Cerebrovascular disease is the first cause of death in Croatia and the third most common cause of death in developed countries. Cerebrovascular disease presents either as transient ischaemic attacks (TIAs) and/or as ischaemic stroke. Thrombi or emboli from ulcerated atheromatous plaques can interrupt intracranial or

extracranial arterial blood supply causing brain ischemia and consequent neurological symptoms. If the blood supply is promptly restored, brain tissue recovers and neurological symptoms disappear. However, if vessel occlusion lasts longer than 1 hour, the result is ischaemic necrosis and permanent neurologic damage.

Transient ischaemic attacks are episodes of sudden, focal neurological dysfunction from a vascular cause, i.e. internal carotid-middle cerebral or the vertebrobasilar arterial system. They last several minutes or, much less often, hours but resolve within 24 hours. Symptoms are identical to those of stroke but are transient.

Stroke can be caused by cerebral ischemia and infarction (85% of all cases), cerebral haemorrhage (10%) or subarachnoid haemorrhage (5%). The hallmark of ischaemic stroke is the sudden onset of focal neurological deficit. The symptoms of ischaemic stroke are related to the location and the volume of brain tissue damaged as well as to the mechanism of injury. For example if the carotid blood supply is compromised and therefore middle cerebral artery becomes occluded, monocular blindness, contralateral hemiparesis and aphasia occur.

Peripheral artery disease (PAD) caused by atherosclerosis is also increasing as the population ages and as patients survive their myocardial infarctions. The pathophysiological basis of PAD is identical to that which occurs in coronary artery atherosclerosis and the same risk factors are associated. PAD can be present as chronic ischaemia that is caused by gradual enlargement of an atheromatous plaque and therefore insufficient blood supply, for example to a limb. The symptom of this entity is intermittent claudication, i.e. pain or cramps that occur on walking and are usually relieved in 1 to 5 minutes by rest after which the patient can walk as far again before pain recurs. Disease progression is marked by a reduction in the distance the patient can walk without pain. Acute ischaemia due to acute artery occlusion is characterized by sudden onset of severe pain, coldness and pallor in an extremity with absent pulses distal to the obstruction.

Recommended literature:

1 Braunwald E. Unstable angina: A classification. Circulation 1989; 80:410-14.

2 Cannon RO. Chest pain with normal coronary angiograms. NEJM 1993; 328:1706-8.

3 Libby P. Molecular basis of the acute coronary syndromes. Circulation 1995; 91:2844-50.

4 Reiner Ž, Tedeschi-Reiner E. Novije spoznaje o patofiziologiji atheroskleroze.Lijec Vjesn 2001; 123:26-31.

5 Ross R. Atherosclerosis – an inflamatory disease. NEJM 1999; 340:115-26.