

Critical Review of Subclinical Atherosclerosis: Perspectives on Medical Imaging Around the Carotid Intima Media

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Abstract: Background and aims: This review article was conducted for educational purposes to address a general overview of subclinical atherosclerosis, with the aim of reducing information bias with valid and reliable data around subclinical atherosclerosis with medical imaging perspectives around the carotid intima media. Methods: The steps summarizing the flowchart of information selection related to the use of engines providing English and French publications between 1997 and 2022 were followed. Results: The given results relevant to the history, morphology, atherogenesis, epidemioclinics (morbidity and mortality), anatomophysiology and morphopathology (circulating markers and biomarkers of endothelial damage, endothelium and structural markers, function of the endothelium, histopathological alterations, pathophysiology/chronobiology/ atherogenesis, etiopathogeny of carotid atherosclerosis by medical imaging/ definition of complex interactions with cardiometabolic markers/mediators. Conclusion: Understanding the stages of atherosclerosis will enable the clinician and radiologist to improve the management of ischemic heart disease, stroke, and peripheral vascular pathology.

Keywords: Atherosclerosis, Medical Imaging, Carotid Intima Media

1. Introduction

Subclinical atherosclerosis (SA) consists of thickening of the carotid intima-media layers detected by ultrasonography [1-4]. In contrast to clinical, overt and advanced atherosclerosis [5-9], SA is a variable combination of intimal and media remodelling in large- and medium-calibre arteries and reflects an inflammatory response to arterial wall injury [1-4]. Unlike clinical, overt

and advanced atherosclerosis [5-9], AthInfraC is a variable combination of intimal and medial changes in large and medium caliber arteries and reflects an inflammatory response to arterial wall injury [1-4]. Indeed, arterial stiffness and carotid intima-media thickness (CIMT) are non-invasive ultrasound indicators of SA or subclinical atherosclerosis, which are associated with cardiovascular disease including stroke and ischaemic heart disease (coronary heart disease) as well as

overall mortality [10, 11]. On the other hand, AthInfraC is different from arteriosclerosis characterised by sclerosis of the muscle fibres of the media and involves arterioles with a process of senescence (advancement in physiological age) [12-15].

The objective of this critical review is to provide a general overview of AthInfraC in order to reduce information bias with valid and reliable data [1-15].

2. The Methods

Figure 1 followed the steps summarising the flowchart of

the selection of information related to the use of engines providing publications in English and French between 1997 and 2022, the choice of keywords according to the specificity of the origin of publication until the final stage of inclusion of the articles included.

Therefore, only evidence published by journals indexed in the evidence-based medicine framework from Google, Google Scholar, Medline (Pub Med) and PMC were considered.

Despite the controversies, limitations and benefits of CIMT on atherosclerosis [8, 16-19], only recent scientific publications were considered in the results sections.

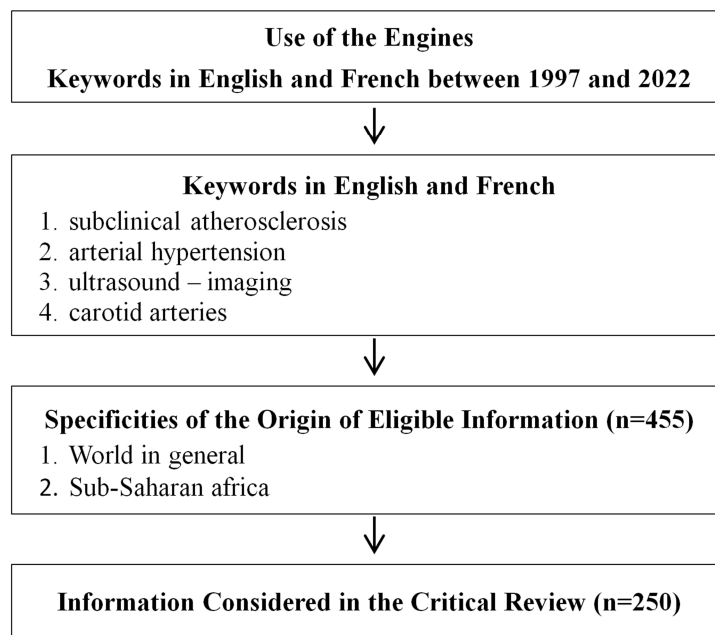


Figure 1. Flowchart for selecting reliable information.

Ethical Considerations

To carry out this study, the protocol was submitted to the scientific committee of the Department of Internal Medicine of the University Clinics of Kinshasa and to the ethics committee of the School of Public Health of the University of Kinshasa acting as the national ethics committee (Approval number: ESP/CE/076/2018).

After explaining the objectives of the study, its conduct, its safety and its merits, informed consent was obtained from the study participants while respecting confidentiality in accordance with the Helsinki protocol.

Translated with www.DeepL.com/Translator (free version).

3. Results

3.1. History, Morphology and Atherogenesis

It was in the first century that Galen reported that arteries were distinct from veins. [20].

After the work of William Harvey in 1628 on blood circulation, many scientists documented the connections between arteries, veins and capillaries [20].

Theodor Schwann described in 1839 the presence of a membrane in the capillaries separating the blood from the tissues and which Wilhelm His named vascular endothelium in 1865 [21].

Thus the cardiovascular system is composed of several well-structured vessels for homeostasis of the organism and for an appropriate response to the various constraints to which it will be subjected. [20, 21].

Atherogenesis means the generation of atherosclerosis during six stadializations [22, 23].

Indeed, atherosclerosis reflects a chronic inflammatory condition accompanied by the deposition of lipids, muscle cells and fibrous elements in the arterial wall. [22, 23].

Evolutionary progression of morphopathological abnormality of atherosclerosis [23, 24] is characterized by the following stages:

Stage 1 defined by the formation of an atherosclerotic lesion with the penetration and accumulation of LDL-Cholesterol and other lipoproteins in the sub-endothelial layer (intima);

Stage 2 is characterized by the formation of lipid streaks with foam cells, smooth muscle cells without the formation

of extra cellular lipids;

Stage 3 corresponds to pre-atheroma with extra cellular lipids and foam cell necrosis;

Stage 4 includes extracellular lipids and intra cellular lipids at the level of simple atheroma;

Stage 5 defines a fibrous web produced by smooth muscle cells full of collagen, fibrin, elastin and myco polysaccharides;

Stage 6a defines rupture of the fibrous cap while stage 6b is manifested by intra-plaque hemorrhage versus stage 6c which defines thrombosis;

Stage 7 includes calcified plaques associated with advancing age;

Stage 8 includes sclerotic plaques.

Stages 1 and 2 are asymptomatic, appear before the biological age of 10 years, stage 3 is considered pre-atheroma while stages 4-8 define the advanced evolution of post plaque [23].

3.2. Epidemioclinical

Its epidemioclinic concerns its long asymptomatic manifestations becoming manifest with morbidity and its prognosis including mortality [25-27].

3.2.1. Morbidity

Cardiovascular disease, including clinical (overt) atherosclerosis, often associated with the metabolic syndrome as part of the cardiometabolic risk, is a real burden according to the World Health Organisation (WHO) in its 2021 update [10].

Indeed, 17.7 million deaths are attributable to cardiovascular disease and account for 31% of total global mortality [10]. Advancing age leads to thickening and narrowing of the blood vessels, which are responsible for cardiovascular disease, which, along with cancer, is the two leading cause of death and reduced life expectancy in adults [28].

Globalisation, the health transition (epidemiological, demographic and nutritional) and uncontrolled urbanisation account for more than three quarters of deaths attributable to cardiovascular disease in low- and middle-income countries [11, 29, 30].

Hypertension, obesity, diabetes mellitus, hyperlipidaemia, advancing age, smoking, psychological stress and sedentary lifestyle are well established as classic factors [31].

However, thrombogenic conditions, homocysteine, markers of inflammation and infection, heredity (genes and susceptibility), chronic kidney disease, and structural markers (medical imaging: thickening/ MICA/subclinical atherosclerosis without plaque versus overt clinical atherosclerosis with plaque) are considered emerging factors [31-35].

Morbidity, disability and the negative socio-economic impact of cardiovascular disease are declining in developed countries under primary, primary, secondary, tertiary and quaternary prevention [36, 37].

Hypertension is a common condition, a silent killer, and above all a proven risk factor for a large number of

potentially serious pathologies: heart failure, stroke, myocardial infarction or even kidney damage that can lead to renal failure [38].

Developing countries, usually confronted with communicable infectious diseases and nutritional disorders, are witnessing the emergence of chronic non-communicable diseases, including cardiovascular disease (CVD), as a result of urbanisation and lifestyle changes, with the consequent epidemiological and nutritional transition [11, 29, 30, 39, 40].

In the Democratic Republic of Congo (DRC), the prevalence of hypertension, which is both a cardiovascular disease (CVD) and a cardiovascular risk factor (CVDRF) in atherosclerosis, was considered rare or even non-existent before 1960 [41, 42].

However, after the 1970s [43], the emergence of arterial hypertension and its complications was highlighted in the general population, certain provinces including Kinshasa, central Congo and the greater East [44-48].

The extent and impact of cardiovascular risk factors, both classic and emerging, are now more established in hospitals than in the general population [34, 39, 44].

The health transition (epidemiological, demographic and nutritional) could explain the prevalence and morbimortality of hypertension in the Democratic Republic of Congo (DRC).

3.2.2. Mortality

Cardiovascular disease (CVD) is the leading cause of death worldwide according to statistics from the World Health Organization (WHO) [10].

In 2008, nearly 17.3 million deaths worldwide were related to cardiovascular disease, this figure is expected to double by 2030 [49].

Of all deaths in low- and middle-income countries, deaths from cardiovascular disease increased by 26-28% between 1990 and 2001 [50], a consequence of a growing epidemiological transition.

Thus developing countries contribute a larger share of global CV mortality compared to developed countries. [26] with socio-economic repercussions negatively impacting these countries and consequently making them poorer.

3.3. Anatomophysiology, Morphopathology

3.3.1. Circulating Markers and Biomarkers

The rate of endothelial turnover is extremely slow, regardless of vascular calibre. Approximately 99% of endothelial cells are in a quiescent state [51-53].

Endothelial damage can be infectious, metabolic, inflammatory or immunological in origin, resulting in chain reactions and the acquisition of a physiological activated phenotype by the smooth muscle cell [51, 52].

Endothelial dysfunction or the development of irreversible parietal damage occurs when the action of the aggressive agent persists or when the physiological control mechanisms of the smooth muscle cell are overridden, leading to pathological damage [51-53].

The manifestations of endothelial damage are multiple and consist of the release of substances, the installation of

complex processes and, in particular, the disunion of the endothelial monolayer [54].

Endothelial damage results in endothelial dysfunction linked to prolonged activation of endothelial cells (type I), which is frequently found in atherosclerosis, inflammatory processes, hypertension and pulmonary arterial hypertension [54], or in the breakdown of vascular integrity (type II and III) during mechanical damage to vascular tissue, resulting in irreversible damage [55].

These endothelial attacks favour the genesis of a pro-thrombotic environment justifying the triggering of vascular pathologies during endothelial alteration [55].

The endothelial reaction cascade (activation-injury-regeneration) generates plasma soluble markers, circulating endothelial cell (CEC) detachment and endothelial microparticle (EMP) formation [33].

3.3.2. Endothelium and Structural Markers

The endothelium is actively involved in many physiological and pathophysiological processes [56, 57].

(i). Endothelial Function

The endothelium regulates vascular tone, cell growth, the inflammatory process via transendothelial migration of leukocytes, vascular permeability and coagulation [57]. It plays an antioxidant role.

a. Vascular tone control

The control of vascular tone is ensured thanks to the secretion of numerous mediators involved in vascular hemodynamics in the physiological state. [57]. The endothelium regulates blood pressure and blood flow by releasing vasodilator molecules [nitric oxide (NO), prostacyclin or prostaglandin I₂ (PGI₂)] and vasoconstrictor molecules [endothelin-1 (ET-1) and platelet-activating factor (PAF)] [57].

NO maintains baseline tone by relaxing smooth muscle cells, inhibits leukocyte adhesion to endothelium, platelet activation, smooth muscle cell migration and proliferation [57].

ET-1, a powerful vasoconstrictor, stimulates cell proliferation and causes contraction of smooth muscle cells [57].

PGI₂ participates in the relaxation of SMCs and prevents platelet aggregation, as well as the proliferation of SMCs. It also has a role in local inflammatory responses [57].

PAF facilitates leukocyte adhesion to the vessel wall.

b. Hemostasis Control

(1) Primary Hemostasis Control

Control of primary hemostasis is ensured on the antithrombotic surface of the endothelium, but this characteristic of the endothelial surface can be altered and become procoagulant under the effect of exogenous mechanical or chemical factors. [57].

Any vascular lesion leads to reflex vasoconstriction and a decrease in blood flow followed by platelet adhesion by binding to sub-endothelial compounds such as collagen; this platelet adhesion can be done directly by glycoproteins (GP) Ia and VI or indirectly by binding of Willebrand factor [57].

In the basal state, NO and PGI₂ inhibit platelet adhesion,

activation, secretion and aggregation resulting in platelet disaggregation [57].

(2) Coagulation Control

The endothelium plays a role in coagulation by controlling the production of thrombin, necessary for the balance between anti and pro coagulant effects. [57].

Thrombin stimulates the procoagulant effect of endothelial cells, the activation of platelets, many coagulation enzymes and their cofactors. Antithrombin binds to heparan sulfates and proteoglycans of the endothelial surface [57]. The release of TFPI (tissue factor pathway inhibitor) by endothelial cells under the action of heparin thus reduces the generation of thrombin [58].

The expression of thrombomodulin by endothelial cells and its binding to thrombin participate in the activation of protein C which interacts with protein S (its cofactor) to exert its anti-coagulant activity by inactivating factors V and VIII. [58]. Thrombomodulin also decreases the activation of platelets, factors V, XIII and fibrinogen by thrombin and stimulates the fibrinolytic activity of ECs.

Thrombomodulin participates in the production of thrombin by inhibiting the activity of factor Xa [58].

The endothelial cell can become procoagulant under the action of inflammatory cytokines.

(3) Fibrinolysis control

In the basal state, the endothelium is pro-fibrinolytic via the secretion of tissue plasminogen activator, t-PA [59]. t-PA is a powerful fibrinolysis activator, allowing the transformation of plasminogen into plasmin which degrades fibrin.

Under the effect of various stimuli [thrombin, endotoxins, certain inflammatory cytokines and oxidized LDL (low-density lipoprotein)], the EC secrete the main inhibitor of t-PA, PAI-1 (plasminogen activator inhibitor 1) in the circulating blood and neutralizes the fibrinolytic activity of t-PA and u-PA (urokinase) produced by cells other than the EC [59].

(4) Inflammation control

Control of inflammation is achieved through the attachment of leukocytes to endothelial cells in areas of low resistance (post-capillary venules) as opposed to platelets which attach to the sub-endothelium of arteries subjected to high shear forces. [59].

ECs synthesize chemokines and express molecules such as PECAM-1 (Platelet/Endothelial Cell Adhesion Molecule) allowing leukocyte transmigration.

(5) Control of vascular permeability

The endothelium constitutes a real barrier to regulate the passage of macromolecules and the circulation of cells from the blood to the tissues. This role is performed by the interendothelial junctions [59].

The endothelium controls cell growth and protein synthesis.

In the basal state, thanks to its anticoagulant, anti-adhesive and vasodilating properties, the endothelium ensures blood fluidity [59].

Any aggression activates the endothelium and triggers the pro coagulant and vasoconstrictor properties and promotes the adhesion of leukocytes and their migration to inflammatory sites. [59].

(ii). Dynamism of the Endothelium

The microenvironment and genetics or epigenetics regulate endothelial functions [60].

The endothelium regulates its functions according to the signals it receives and whose response to the same signal varies according to its intrinsic properties (determined by their genetic programming).

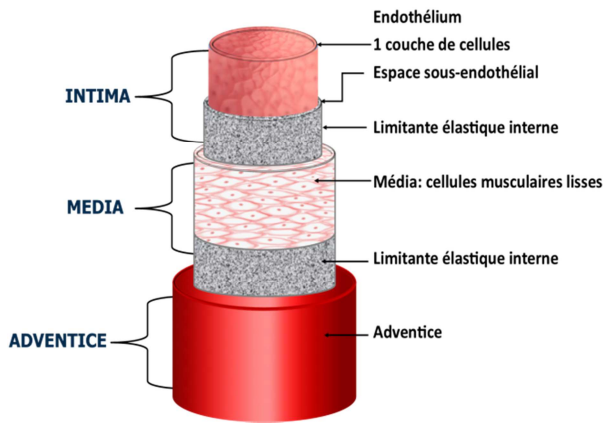


Figure 2. Structure of the vascular wall.

Similarly, the endothelium exerts control over the environment. The phenotype of ECs varies in time and space depending on signals from the extracellular environment and adjacent cells [60]. Endothelial dysfunction corresponds to an endothelial response that is not adapted and therefore harmful to the individual, whether local or systemic. [60].

(iii). Vascular Wall Structure

The vascular wall consists of three layers namely the intima, the media and the adventitia stratified from the endoluminal cavity towards the periphery of the artery [56, 57].

The intima is the inner layer of the arterial wall, made up of a monolayer of endothelial cells (EC) of about 15 μm , resting on a basement membrane.

The internal elastic lamina is made up of elastic fibers and separates the intima from the media [56, 57].

The media is the middle layer, considered the main arterial layer made of a concentric juxtaposition of lamellar units formed of smooth muscle cells (SMC) and a connective matrix (elastin, collagen and mucosaccharides) [56, 57].

The external elastic lamina made up of fenestrated elastin blades separates the media from the adventitia, this fenestration allows the bidirectional passage of substances and cells.

The adventitia, outer coat, is made up of basal connective tissue, fibroblasts, fat cells and *willandnervi vasorum* [56, 57]. The importance of these three tunics is variable according to the type of vessels, and conditions their functions [56, 57].

There are three types of arteries namely elastic or conductive arteries, muscular arteries and arterioles [56, 57].

The elastic arteries are large arteries, with a highly developed media, rich in elastic fibers, collagen and muscle fibers. These arteries are close to the heart and have little resistance to flow [56, 57].

The muscular arteries or distributing arteries are medium

caliber arteries with a media rich in smooth muscle and less supplied with elastic fibers with as a corollary the great capacity of vasoconstriction and vasodilation, necessary for the regulation of blood flow to the tissues. [56, 57].

Arterioles are the smallest arteries, located in the tissues before the capillaries.

Capillaries have a very small diameter, are located around the cells in the tissues between arterioles and venules. They ensure the exchanges between the blood and the cells [56, 57].

Venules are small veins formed by the union of several capillaries, collect blood from the capillaries and discharge it into the veins. Venules close to capillaries are composed of endothelium and some SMCs while those close to veins have an outer coat similar to that of veins [56, 57].

The veins have a very large diameter, rich in collagen and less supplied with smooth muscle fibers and are made up of three tunics than the arteries but their relative thickness is different. The venous circulation is a return circulation and constitutes a real blood reservoir [56, 57].

3.3.3. Histopathological Alterations

There are three types of lesions (pre atherosclerosis, uncomplicated atherosclerosis, and complicated atherosclerosis) which progress through subsequent stages of the atherosclerotic process [57]:

1. the lipid streak and the gelatinous plaque;
2. fibrolipid plaque (fibroatheroma);
3. complicated lesion.

(i). Initial Pre-atherosclerotic Lesions

The involvement of the intimal pads, fatty streaks and pre-atheroma define the initial pre-atherosclerotic lesions [56].

a. The intimal pads

During intrauterine life appears an intimal fibromuscular thickening composed of smooth muscle cells, which migrate from the media to the subendothelium where they proliferate, creating purely histological focal lesions (intimal pads), thus constituting precursors of atherosclerosis [57].

There is no morphological modification of the arterial lumen and no lipids in the smooth muscle cells or in the extracellular space [57].

b. Lipid streaks

The streaks appear at different stages of life: in the thoracic and abdominal aorta and in the carotid system from childhood, in the coronary arteries from adolescence (12 to 14 years old) [61].

The streaks are made up of deposits of lipids essentially of blood origin. Endothelial elevation is caused by the presence of foam cells and extracellular deposits of lipids in the intima [61]. The endothelium is intact, there are no interstitial inflammatory reactions.

The streaks do not necessarily evolve towards the formation of an atherosclerotic plaque but seem to be the starting point for more advanced atherosclerotic lesions (atherosclerotic plaque).

c. Pre-atheroma

Pre-atheroma is formed from changes in the lipid streak following the abundant deposition of extracellular lipids [61].

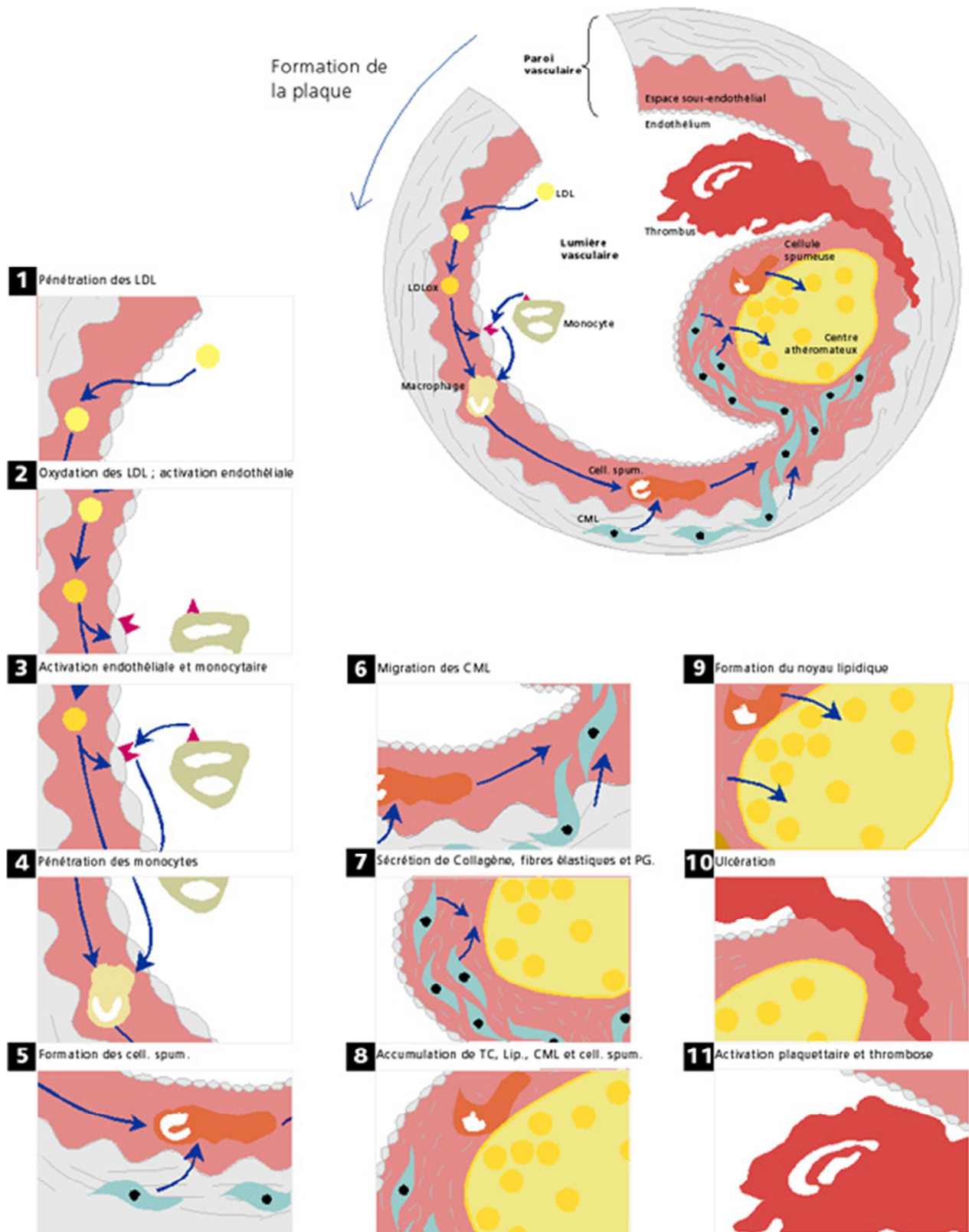


Figure 3. Diagram representing the different stages of atherosclerosis taken from reference No. 61.

(ii). Uncomplicated Mature Atherosclerotic Plaques

With regard to the uncomplicated plaque, the anatomical changes settle during the first ten years of life in the form of

a fatty streak which evolves into the atheromatous pustule. [62–65]. This is the formed and uncomplicated plaque comprising the fibrolipid layer at the initial stage followed by the appearance of intimal necrosis which will extend in depth

towards the media. [66, 67].

Indeed, the formed plate comprises a fibrous peripheral

framework surrounding a fatty center composed of foam cells, extracellular lipid deposits and cellular debris.

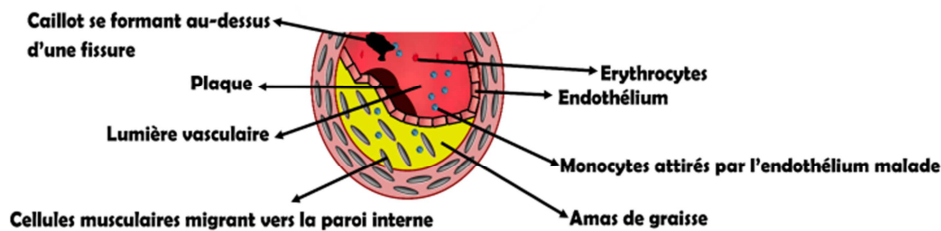


Figure 4. Adult atherosclerotic plaque.

Bends, branches and arterial bifurcations are preferential sites of atherosclerotic lesions (abdominal aorta, coronary arteries, arteries of the lower limbs, descending thoracic aorta and supra aortic trunks) [61].



Figure 5. Atherosclerotic plaques in the coronary arteries.

(iii). Complicated Atherosclerotic Plaques

The clinical expression of complicated atherosclerotic plaque includes stenosis, hemorrhage, ulceration, thrombosis, embolism and aneurysm [61].

a. The stenosis

It is responsible for the narrowing of the arterial lumen caused by the protrusion of the atherosclerotic plaque with the consequence of a reduction in blood flow resulting in downstream ischemia (angina pectoris or intermittent claudication depending on the topography) [61].

b. The hemorrhage

It results from the rupture of new vessels irrigating the plaque and the media or from the penetration of blood from the arterial lumen through a breach opened by the ulceration of the plaque.

Hemorrhage is complicated by atheromatous dissecting hematoma and dissecting aneurysm [68].

c. Ulceration

Main complication of atherosclerosis, it corresponds to the fracture of the plaque with a rupture of the endothelium and the fibrous cap with opening in the vascular lumen of its necrotic center rich in cellular debris and cholesterol crystals predisposing to embolisms atheromatous [68].

d. Thrombosis

It leads to the construction of a thrombus formed by a platelet aggregate consolidated by a network of fibrin in the lumen of the vessel [68].

Initially the thrombus is white, fibrino-platelet followed by a stratification to become mixed.

The thrombus thus formed can be partially or totally occlusive or it can detach and create an arterial embolism in the downstream territory [61, 68].

Thrombosis is responsible for the most serious clinical manifestations of coronary heart disease and myocardial infarction.

e. The embolism

It can be platelet or atheromatous.

Platelet embolism plays a role in the genesis of ischemic syndromes complicating coronary atherosclerosis [61, 69].

Atheromatous embolism often goes unnoticed but can lead to severe ischemic necrosis [61, 68].

f. The aneurysm

All structures of the arterial wall can be responsible for complications of atherosclerosis.

The internal elastic lamina can rupture, the muscle fibers of the media can dislocate, the adventitia can thicken and infiltrate inflammatory cells [61, 68].

3.4. Physiopathology, Chronobiology and Atherogenesis

Chronobiology is an emerging science interested in the biological rhythm of living organisms with biological clocks specific to speciation [69].

Any dysregulation of chronobiology causes sleep disorders, metabolic syndrome, obesity, diabetes mellitus and acute cardiovascular risk based on atherosclerosis [70].

3.4.1. Senescence and Vascular Age

(i). Vascular Age

The weight of age also impacts an individual's arteries.

In the concept of advancing age (eg aging) due to thickening and narrowing of the vessels during cardiovascular diseases and cancers [28,71].

The vascular age is estimated from a total of points relating to the real biological age according to sex, smoking status, the presence of diabetes mellitus, the level of systolic pressure, the concentration of total cholesterolemia and the concentration of HDL-cholesterolemia [28].

Thus the difference between the vascular age-actual biological age ≥ 10 years determined the high cardiovascular risk (stroke, ischemic heart disease).

The age of the arteries increases when the blood vessels

are subjected to several aggressions such as hypertension, tobacco, diabetes mellitus and too high cholesterol [28].

By assessing "the age of his arteries", each hypertensive will know the importance of damage to his vessels. It will then be possible to advise on treatments more suitable, which will allow maintain the age of their arteries as close as possible their actual biological age, allow an advancement in age close to good health (senescence: healthy aging) [28,71].

It also makes it possible to quantify the benefit provided by stopping smoking if you smoke, or by the drop in blood pressure or cholesterol induced by the treatments.

(ii). Vascular Senility

Pathological senescence of the vessels is called vascular wall senility and results in structural changes in elastin, stiffening of collagen and alteration of arterial vasomotility, resulting in a decrease in arterial compliance and an increase in systolic blood pressure with age higher than that of diastolic blood pressure, causing an increase in the differential [71].

Early arterial senility is characterized by a more rapid evolution of vascular alteration in a given subject compared to the population of the same age. [72].

Arterial senility is assessed by measuring arterial stiffness, reflecting a decrease in arterial parietal compliance, measuring carotid intima media thickness, reflecting a remodeling of the intima and media, and finally by search for atherosclerotic plaques [73].

3.4.2. Vascular Remodeling

Arterial remodeling defines the ability to control the existing balance between vasodilation and vasoconstriction in response to certain aggressions until the advent of alterations in the structure of the arterial wall [74, 75].

Among the aggressions, arterial hypertension causes arterial remodeling which includes four cellular processes including cell growth with local vasoactive substances, apoptosis (programmed cell death), cell migration and the production or degradation of the matrix extra cellular in front of certain hemodynamic stimuli [74, 75].

(i). Etiopathogenesis of Arterial Remodeling in Arterial

a. Hypertension

Two types of arterial modification in response to high blood pressure are able to reduce arterial lumen through arterial hypertrophy according to increased wall volume [74, 75].

This increase in the volume of the wall constitutes the compensatory capacity called arterial remodeling. [74, 75].

Arterial remodeling is the source of ultra-structural and geometric modifications within large, medium and small caliber arteries and also the source of numerous pharmacological applications (therapeutic approach/new pharmacological targets, growth factors and specific receptors for smooth muscle cells and without forgetting receptors and enzymes of the extra cellular matrix on the resistive arteries) [74, 75].

Resistive arteries include arterioles and capillaries (microcirculation) are highly rigid to dampen vascular

pulsatility in the face of continuous blood flow.

These resistive arteries distribute this blood flow to peripheral tissues and are regulated by vasomotion [61, 76].

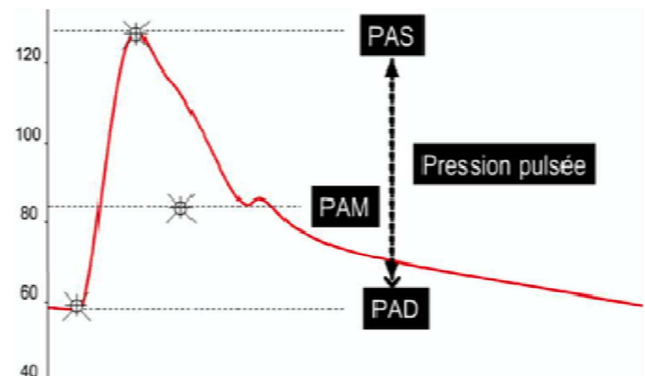


Figure 6. Blood pressure curve.

Arterial catheterization shows a blood pressure curve schematically mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (PAD) and pulse pressure (PP).

b. Systolic Blood Pressure (SBP)

In front of the heart, pump, the systolic arterial pressure reflects the systolic ejection volume (SEV) and the inotropism assessed by the ratio dp/dt (this ratio, slope of the acceleration of the pulse wave).

The faster the blood is ejected with a large blood volume, the more the SBP is increased and the more the blood is ejected with speed and the greater the inotropism becomes. [76].

Arterial compliance is also a determinant of SBP because the stiffer or less compliant the arteries, the higher the SBP. [76].

Advancing age, diabetes mellitus and arterial hypertension amplify the rise in SBP.

c. Diastolic Blood Pressure (PAD)

PAD is one of the determinants of coronary perfusion pressure ($Perf_{co} = PAD - PTV_{VG}$) [76].

The PAD depends on the heart rate, when the diastolic time shortens, the less time there will be for the BP to drop at the end of systole and therefore the more the PAD is increased.

Moreover, bradycardia (decrease in heart rate < 55 beats / minute) in athletes and cardiac surgery patients presents a conduction disorder with a decrease in PAD [76].

This situation of loss of arterial compliance explains the decrease in coronary perfusion in the face of left ventricular hypertrophy, myocardial infarction, 3rd degree atrioventricular block and sepsis (vasoplegia and tachycardia).

This is why the decrease in PAD follows a steep slope expressed mathematically by the "Tau" coefficient. [76].

Pulse pressure (PP)

Pulse pressure or differential pressure calculated by $PAS - PAD$ explained by the following determinants: arterial compliance and stroke volume (end diastolic volume – end systolic volume) [76].

Enlarged PP reflects hypovolemia while pinched or reduced PP also reflects hypovolemia with heart pump failure [76].

d. Mean Arterial Pressure (MAP)

In an arterial system with non-pulsatile blood flow (modification of PAS and PAD), MAP determines the perfusion pressure of noble and functional organs including coronary arteries [76].

(ii). Etiopathogenesis of Carotid Atherosclerosis by Medical Imaging and Definition of Complex Interactions with Cardiometabolic Markers/Mediators

Several etiopathogenic mechanisms of the adaptive to the pathological status of the thickening of the arterial wall appear when the arterial pressure and the pulsatile blood flow which vary according to the cardiac pulsations, subject the endothelium to the various hemodynamic constraints like the hydrostatic pressure, the cyclic stretching and shear forces [77].

Endothelial cells and smooth muscle cells make up the vascular wall and contain receptors that can sense and respond to said hemodynamic stresses/forces.

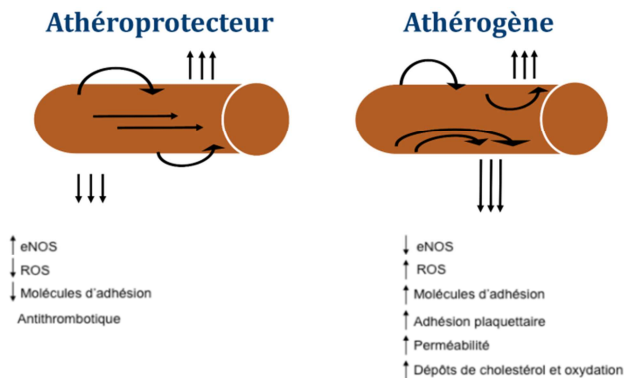


Figure 7. Effects of hemodynamic forces on endothelial functions.

ROS: reactive oxygen species; eNOS: endothelial nitric oxide synthase.

(iii). Hemodynamic Constraints

a. Hydrostatic pressure as hemodynamic constraint

The hydrostatic pressure, pressure that the blood exerts on the vascular walls, is accompanied by the pulsatile pressure gradient between 120 mm Hg and 100 mm Hg in the aorta and between 0 mm Hg and 30 mm Hg in the microcirculation [21, 78] is proportional to arterial diameter [79–81].

The hydrostatic pressure, stress or hemodynamic force acts on the arterial structure and increases in proportion to the production of smooth muscle cell hypertrophy and the increase in the amount of extracellular matrix in the vascular wall. [77, 82].

Indeed, any stress exerted on the arterial wall is the result of the tension divided by its thickness which tries to reduce the stress undergone by this parietal thickening. [77].

Thus, parietal thickening constitutes an adaptive process [77].

b. Cyclic stretch as hemodynamic constraint

Cyclic stretching constitutes a force perpendicular to the

arterial wall and characterized by the circumferential deformation of this arterial wall which is associated with distension and its relaxation during the cardiac cycle [21, 78, 83].

The cyclic stress is estimated at 2% in the aorta contrary to the pathological cyclic stress in hypertension and > 30% in the aorta [21, 78].

It is well established that endothelial cells are normally oriented perpendicular to the stretching axis to reduce the mechanical resistance of the endothelium in the face of significant deformation in the event of the parallel orientation of the endothelium towards the stretching forces. [21, 84], which causes elevation of cyclic stress accompanied by increased expression of matrix metallo proteinase (MMP), a proteolytic enzyme that degrades the arterial basement and interstitial membrane as part of the arterial remodeling process [83].

c. Shear forces as hemodynamic stress

The shearing forces or frictional stress exerted by the blood flow on the endothelial cells are estimated to be optimal between 10 dynes/cm² and 25 dynes/cm² [21, 85].

At constant blood viscosity, shear forces are often regulated by blood flow and arterial lumen diameter [86, 87].

On the other hand, any modification of the shear forces induced on the arterial wall influences the balance between the synthesis of the extra cellular matrix within the smooth muscles and the degradation of the extra cellular matrix within the smooth muscles by the metallo proteinase matrix. [80, 88, 89].

What causes the arterial positive remodeling process linked to an enlargement of the arterial lumen in front of the elevation of shear forces [85, 89].

However, the decrease in shear forces causes the thickening of the arterial wall concomitantly with the decrease in the arterial lumen as part of the process of pro-atherogenic negative remodeling. [24, 90].

d. Complex of Shear Forces and Adaptive Remodeling

There are several cellular activities determined by said hemodynamic forces induced on the cells of the vascular wall [80, 88, 91–93]:

decrease in the production of nitric oxide (NO);

increased production of endothelin-1, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) promoting migration, differentiation and proliferation of vascular smooth muscle cells.

What promotes arterial thickening via the effect of shear forces in the distribution and function of vascular smooth muscle cells [92, 93].

Furthermore, this hemodynamic change not only disrupts smooth muscle cells but the decrease in shear forces promotes an elevation of platelet aggregation and endothelial dysfunction, apoptosis and infiltration of attached low density lipoproteins (LDL). lipid-carrying macromolecules in blood plasma [67, 89, 94].

After LDL particles cross the endothelial cell layer, they develop oxidation which further stimulates smooth muscle cell proliferation and extracellular matrix (proteoglycan) synthesis. [89, 95, 96].

The microenvironment (LDL particles-endothelial dysfunction-LDL oxidation) promotes the establishment of an inflammatory milieu under the activation of nuclear transcription factor kappa B (NF- κ B) [92, 93].

Indeed, NF- κ B is involved in the regulation of the expression of inflammatory molecules and adhesion molecules (Monocyte chemoattractant protein-1: MCP-1)

and vascular cell adhesion molecule-1 (VCAM-1).

Finally, said adhesion molecules promote the recruitment of mononuclear leukocytes (monocytes and T lymphocytes) which migrate into the intima [80, 97, 98].

Once internalized in the intima, monocytes evolve into macrophages (Reference) which ingest oxidized LDL particles to be transformed into foam cells in atherosclerosis [97].

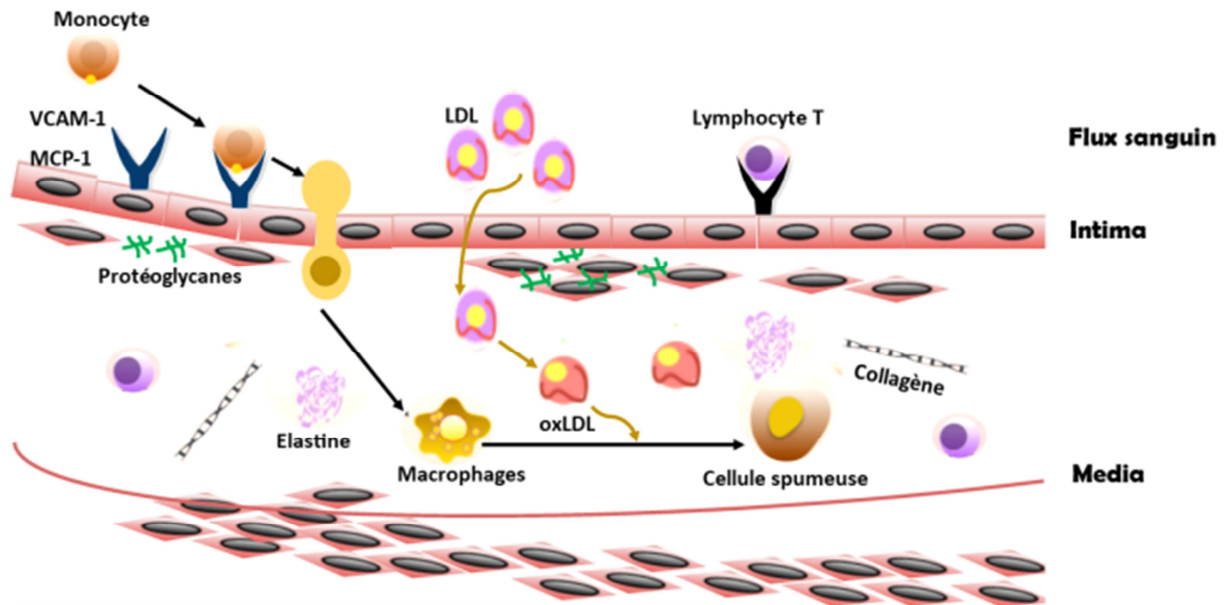


Figure 8. Initiation of atherosclerosis (figure adapted from Libby *et al.*, reference N°97).

VCAM-1: vascular adhesion molecule-1; LDL: low density lipoproteins; oxLDL: oxidized LDL;

Arterial remodeling, the process of adaptive arterial parietal thickening, promotes an increase in the number of smooth muscle cells (hyperplasia) or in size (vascular hypertrophy).

Vascular hyperplasia is defined by the increase in cell division towards the uniform accumulation of smooth muscle cells or microfibroblasts without lipid accumulation [81].

On the other hand, arterial fibromuscular hypertrophy is characterized by an increase in the size of smooth muscle cells with a moderate accumulation of lipids. [81].

Adaptive intimal thickening is diffuse or eccentric [99].

Diffuse thickening occurs at arterial segments without branches [79, 99].

The entire circumference of the vessel can be invaded by the musculoelastic thickening circumferentially and longitudinally in consideration of the absence of lipids in the cell hyperplasia [79, 99].

Eccentric thickening is found where stresses are not evenly distributed with local thickening greater than diffuse thickening [81].

3.5. Carotid Intima-Media Thickness (EIMc), Marker of Cardiovascular Risk

3.5.1. Clinical Estimation of Cardiovascular Risk

The NCEP (National Cholesterol Education Program) III recommends the Framingham score to estimate risk at 10 years of duration of coronary or heart attack myocardium [100].

This score takes into account as parameters the age, gender, cholesterol level total and HDL cholesterol, the level of systolic and diastolic pressure, the existence or not of smoking, the presence or not of a disease.

The limitations of this score consist in the fact that it does not evaluate the importance or the seniority of smoking and diabetes, and CV risk is assessed at 10 years and not over time of life:

1. women who later develop CV disease can be classified as low CV risk despite impairment silent subclinical;
2. patients presenting a single FDR but of a very high level can be subclassed;
3. the family history of early CV disease are not taken into account;
4. certain FDR such as smoking or diabetes are denoted without gradation, while there is a continuum between the level FDR and RCV;
5. this is the first Framingham score FDR that ignores individual variations in load at advanced age [101].

3.5.2. Clinical and Ultrasound Estimation of Cardiovascular Risk

The RCV evaluated by eight prospective studies that each included more than 1,000 subjects [102–104] showed that the EIMc is significantly associated with risk of heart attack myocardium, stroke, mortality coronary.

The relationship between increased ADR and incidence of CV events has been established over a wide age range, but the strongest data is in the age groups 42-74 years. [100, 105].

3.5.3. Intermediate Risk Estimate

The measurement of the EIM and the distal protection of carotid plaques are relevant in the assessment of CVRS in subjects classified as low or intermediate risk by the NCEP III Framingham score but presenting with a high level FDR [105–107]:

1. antfamily history of early CV disease in first-degree relatives (male < 55 years old, female < 65 years old);
2. subjects < 60 years old with an isolated FDR but of severe intensity, for example a dyslipid starcrumb gstarnotstartick;
3. women < 60 years with at least two cardiovascular risk factors.

3.5.4. Association Between EIMc and Cardiovascular Risk Factors

(i). Traditional Risk Factors

Several studies have reported a significant correlation between the degree of cADE and other traditional CV risk factors. [108]. Age and elevation of BP, two main determinants of cIME in the general population, greatly influence the progression of atherosclerosis. Beyond these two factors, other pro-atherogenic factors such as total cholesterol, low density cholesterol (LDL-cholesterol) and insulin resistance are also significantly associated with cEMI. [8, 109–111].

These associations between EIMc and traditional risk factors suggest that EIMc offers the opportunity to be used as a surrogate marker for the prediction of CV events.

To this end, several prospective studies have reported an absolute risk per year of CV events ranging from 1.6% to 3.2% with an increase in the EIMc. The results of these studies clearly indicated that cADE was closely associated with other traditional CV risk factors. [109, 110].

(ii). Emerging Risk Factors

EIMc, hypertension, chronic kidney disease, cardio-renal syndrome, micro albuminuria, inflammation/infection, endothelial reactivity and dysfunction, emerging cardiovascular risk factors, are currently implicated in atherosclerosis [57, 112–114].

The vascular endothelium, voluminous paracrine gland of the body has a secretory activity, cell transfers and regulation of vasomotion [74, 78].

Endothelial dysfunction, cause and consequence of the chronic increase in blood pressure figures, is therefore closely associated with vascular inflammation and oxidative stress, and represents the early stage of atherogenesis. [115].

Inflammation plays a key role in the pathogenesis of atherosclerotic disease.

PCR, a systemic marker of inflammation, is the witness of an acute but also chronic inflammatory reaction at low noise. [34].

Several studies have focused on PCR as an early marker and actor of atherogenesis, particularly in coronary artery disease. [116].

The association between cEMI and CRP is well established.

However, many limitations and confounding factors increase CRP levels.

At present, the screening of classic risk factors takes precedence over that of biological markers in the evaluation of individual CVD [33].

Detection of microalbuminuria is an early indicator of subclinical microvascular complications of renal glomeruli in diabetic and hypertensive patients [117].

Moreover, it is also associated with a high risk of atherosclerotic diseases in these patients.

Several studies have reported the independent association between micro albuminuria (marker of micro vascular dysfunction) and indices of macro vascular complications such as IPS, cEIM and PCR in patients with type 2 diabetes mellitus and hypertension. essential [34, 114].

Other studies have shown opposite results especially for the association between microalbuminuria and EIMc [61].

4. Conclusion

This systematic review has emphasized the importance of the necessary morphopathological, physiopathological, biopathological and radiological modifications of atherogenesis.

Thus, this understanding of the stages of atherosclerosis will help the clinician and the radiologist, able to improve the management of ischemic heart disease, stroke and peripheral vascular pathology.

References

- [1] Erbel R, Delaney JAC, Lehmann N, McClelland RL, Möhlenkamp S, Kronmal RA, et al. Signs of subclinical coronary atherosclerosis in relation to risk factor distribution in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR). *Eur Heart J.* 2008; 29 (22): 2782–2791.
- [2] Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. *Traffic.* 2009; 119 (3): 382–389.
- [3] Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol.* 2015; 65 (11): 1065–1074.
- [4] Gibson AO, Blaha MJ, Arnan MK, Sacco RL, Szklo M, Herrington DM, et al. Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. *JACC Cardiovascular Imaging.* 2014; 7 (11): 1108–1115.

- [5] Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. *Traffic*. 2014; 129 (1): 77–86.
- [6] Zavadni AEH, Wasserman BA, McClelland RL, Gomes AS, Folsom AR, Polak JF, et al. Carotid artery plaque morphology and composition in relation to incident cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Radiology*. 2014; 271 (2): 381–389.
- [7] Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circ Res*. 2016; 118 (4): 535–546.
- [8] Bots ML, Evans GW, Tegeler CH, Meijer R. Carotid Intima-media Thickness Measurements: Relations with Atherosclerosis, Risk of Cardiovascular Disease and Application in Randomized Controlled Trials. *Chin Med J (Engl)*. 2016; 129 (2): 215–226.
- [9] Boateng D, Agyemang C, Beune E, Meeks K, Smeeth L, Schulze MB, et al. Cardiovascular disease risk prediction in sub-Saharan African populations - Comparative analysis of risk algorithms in the RODAM study. *Int J Cardiol*. 2018; 254: 310–315.
- [10] World Health Organization. *WHO list of priority medical devices for management of cardiovascular diseases and diabetes*. 2021. Geneva. World Health Organization <https://apps.who.int/iris/handle/10665/341967>. Accessed March 5, 2022.
- [11] Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. *Too Med Int Health*. 2008; 13 (10): 1225–1234.
- [12] McGrath JC, Deighan C, Briones AM, Shafaroudi MM, McBride M, Adler J, et al. New aspects of vascular remodeling: the involvement of all vascular cell types. *Exp Physiol*. 2005; 90 (4): 469–475.
- [13] O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol*. 2007; 50 (1): 1–13.
- [14] O'Rourke MF. Arterial aging: pathophysiological principles. *Vasc Med*. 2007; 12 (4): 329–341.
- [15] London GM, Drueke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int*. 1997; 51 (6): 1678–1695.
- [16] Kulshreshtha A, Goyal A, Veledar E, McClellan W, Judd S, Eufinger SC, et al. Association between ideal cardiovascular health and carotid intima-media thickness: a twin study. *J Am Heart Assoc*. 2014; 3 (1): e000282.
- [17] Polonsky TS, Ning H, Daviglus ML, Liu K, Burke GL, Cushman M, et al. Association of Cardiovascular Health With Subclinical Disease and Incident Events: The Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017; 6 (3): e004894.
- [18] Shpilsky D, Bambs C, Kip K, Patel S, Aiyer A, Olafiranye O, et al. Association between ideal cardiovascular health and markers of subclinical cardiovascular disease. *Clin Cardiol*. 2018; 41 (12): 1593–1599.
- [19] el-Barghouti N, Elkeles R, Nicolaides A, Geroulakos G, Dhanjil S, Diamond J. The ultrasonic evaluation of the carotid intima-media thickness and its relation to risk factors of atherosclerosis in normal and diabetic population. *Int Angiol*. 1997; 16 (1): 50–54.
- [20] Hwa C, Aird WC. The history of the capillary wall: doctors, discoveries, and debates. *Am J Physiol Heart Circ Physiol*. 2007; 293 (5): H2667–2679.
- [21] Creager M, Beckman J, Loscalzo. *Vascular Medicine: A Companion to Braunwald's Heart Disease - 3rd Edition*. <https://www.elsevier.com/books/vascular-medicine-a-companion-to-braunwalds-heart-disease/creager/978-0-323-63600-1>. Accessed March 2, 2022.
- [22] Libby P. *The Pathogenesis, Prevention, and Treatment of Atherosclerosis | Harrison's Principles of Internal Medicine, 19th | Access Pharmacy | McGraw Hill Medical*. Harrison's Principles of Internal Medicine, 19th. 2015 <https://accesspharmacy.mhmedical.com/content.aspx?bookid=1130&ionid=79743366>. Accessed March 2, 2022.
- [23] Dubreuil E. *Diet and atherosclerosis*. 2013; not specified.
- [24] Dajnowiec D, Langille BL. Arterial adaptations to chronic changes in haemodynamic function: coupling vasomotor tone to structural remodeling. *Clin Sci (London)*. 2007; 113 (1): 15–23.
- [25] World Health Organization. Cardiovascular diseases (CVDs). 2017. [https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)). Accessed March 2, 2022.
- [26] Mbewu A, Mbanya JC. *Cardiovascular Disease in Disease and Mortality in Sub-Saharan Africa. In CVD in Africa*. 2nd ed. 2006. Washington (DC). World Bank.
- [27] Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *The Lancet*. 2021; 398 (10304): 957–980.
- [28] Professor Jean-Jacques Mourad. Calculate the age of your arteries. French committee for the fight against arterial hypertension..
- [29] Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization. *Globalization and Health*. 2009; 5 (1): 9.
- [30] Belue R, Okonor T, Iwelunmor J, Taylor K, Degboe A, Agyemang C, et al. An overview of cardiovascular risk factor burden disease o-morbidity between infectious disease and chronic disease in sub-Saharan African countries: a socio-cultural perspective. 5: 10.
- [31] Wood D, Joint European Societies Task Force. Established and emerging cardiovascular risk factors. *Am Heart J*. 2001; 141 (2 Suppl): S49–57.
- [32] Takiuchi S, Kamide K, Miwa Y, Tomiyama M, Yoshii M, Matayoshi T, et al. Diagnostic value of carotid intima-media thickness and plaque score for predicting target organ damage in patients with essential hypertension. *J Hum Hypertens*. 2004; 18 (1): 17–23.

- [33] Herinirina NF, Rajaonarison LHNON, Herijoelison AR, Ahmad A. Carotid intima-media thickness and cardiovascular risk factors. *The Pan African Medical Journal*. 2015; 21 (153). doi: 10.11604/pamj.2015.21.153.6876.
- [34] Businge CB, Longo-Mbenza B, Adeniyi OV, Muaka MM, Lelo GM, Nkanga MSN, et al. Diagnostic performance of several biomarkers for identification of cases of non-communicable diseases among Central Africans. *Afr Health Sci*. 2018; 18 (4): 909–916.
- [35] Talari HR, Moniri R, Mollaghanbari M, Haddad Kashani H, Jalalian MN. Evaluating the relationship between *Helicobacter pylori* infection and carotid intima-media thickness a cross sectional study. *Ann Med Surg (London)*. 2021; 69: 102659.
- [36] World Health Organization. Regional Office for the Eastern Mediterranean. List of basic sources in English for a medical faculty library. 2008. <https://apps.who.int/iris/handle/10665/119878>. Accessed March 5, 2022.
- [37] BZ, PP, Ga M, M E. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nature reviews Cardiology*. 2021; 18 (11). doi: 10.1038/s41569-021-00559-8.
- [38] Blacher J, Olié V. Hypertension and renal disease: a relationship under close surveillance. *The kidney disease patient magazine*. 2020; 35.
- [39] Delisle H, Faber M, Revault P. Evidence-based strategies needed to combat malnutrition in Sub-Saharan countries facing different stages of nutrition transition. *Public Health Nutr*. 24 (12): 3577–3580.
- [40] Lofandjola Masumbuku J, Sumaili Kiswaya E, Mairiaux P, Gillain D, Petermans J. Chronic illness needing palliative care in Kinshasa hospitals, Democratic Republic of the Congo (DRC). *Too Med Health*. 2017; 45: 11.
- [41] Vandeputte M. coronary atherosclerosis in Congolese. 1958.
- [42] Longo-Mbenza B, Ngoma DV, Nahimana D, Mayuku DM, Fuele SM, Ekwanzala F, et al. Screen detection and the WHO stepwise approach to the prevalence and risk factors of arterial hypertension in Kinshasa. *Eur J Cardiovascular Prev Rehabil*. 2008; 15 (5): 503–508.
- [43] Tshiani K, Musuamba M. Epidemiology of arterial hypertension in Zaire. Results of a preliminary survey in 4988 subjects. *Med Afr Noire*. 1979; 26: 65–75.
- [44] M'Buyamba-Kabangu J, Disashi T, Kayembe PK, Buila N, Lepira FB. Pulse pressure, renal function and mortality in hospitalized Congolese patients with arterial hypertension. *African annals of medicine*. 2009; 2 (3): 231–239.
- [45] Lepira F, Kayembe P, M'buyamba-Kabangu J, Nseka M. Clinical correlates of left ventricular hypertrophy in black patients with arterial hypertension. *Cardiovascular journal of South Africa: official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners*. 2006.
- [46] Atoba B, Kayembe T, Batina A, Mbo M, Ngandu W, Tsongo K, et al. Prevalence, knowledge and degree of control of arterial hypertension in Kisangani, DR Congo. *Medical journal of research information and medical education*. 2004; 5 (2): 86–93.
- [47] Ngombe LK, Cowgill K, Monga BB, Ilunga BK, Stanis WO, Numbi OL. Prevalence of arterial hypertension in the population of millers in the city of Lubumbashi, Democratic Republic of Congo. *Pan Afr Med J*. 2015; 22: 152.
- [48] M'Buyamba-Kabangu JR, Biswika RT, Thijs L, Tshimanga GM, Ngalula FM, Disashi T, et al. In-hospital mortality among black patients admitted for hypertension-related disorders in Mbuji Mayi, Congo. *Am J Hypertens*. 2009; 22 (6): 643–648.
- [49] Mathers CD, Lopez AD, Murray CJL. The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ, editors. *Global Burden of Disease and Risk Factors*. 2006. Washington (DC). World Bank <http://www.ncbi.nlm.nih.gov/books/NBK11808/>. Accessed March 5, 2022.
- [50] Organization Mundial de la Salud. *Genero, climatic and healthy climate*. 2016. Ginebra. Organization Mundial de la Salud <https://apps.who.int/iris/handle/10665/204178>. Accessed March 5, 2022.
- [51] Piccin A, Murphy WG, Smith OP. Circulating microparticles: pathophysiology and clinical implications. *Blood Rev*. 2007; 21 (3): 157–171.
- [52] Mutin M, Canavy I, Blann A, Bory M, Sampol J, Dignat-George F. Direct evidence of endothelial injury in acute myocardial infarction and unstable angina by demonstration of circulating endothelial cells. *Blood*. 1999; 93 (9): 2951–2958.
- [53] Ingram DA, Mead LE, Moore DB, Woodard W, Fenoglio A, Yoder MC. Vessel wall-derived endothelial cells rapidly proliferate because they contain a complete hierarchy of endothelial progenitor cells. *Blood*. 2005; 105 (7): 2783–2786.
- [54] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med*. 1992; 326 (4): 242–250.
- [55] Sumpio BE, Riley JT, Dardik A. Cells in focus: endothelial cell. *Int J Biochem Cell Biol*. 2002; 34 (12): 1508–1512.
- [56] Mauge L. Physiology of the circulating endothelial compartment in pulmonary arterial hypertension and prospects for the development of a cell therapy product. 201.
- [57] Lucano M. Role of the endothelial cell in atherosclerosis. 1997; 187.
- [58] Broze GJ, Girard TJ. TISSUE FACTOR PATHWAY INHIBITOR: STRUCTURE-FUNCTION. *Front Biosci*. 2012; 17: 262–280.
- [59] Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood*. 1998; 91 (10): 3527–3561.
- [60] Aird WC. Endothelial cell heterogeneity. *Crit Care Med*. 2003; 31 (4 Suppl): S221–230.
- [61] Cohen A. *Cardiology and vascular pathology - Ariel Cohen - Librairie Eyrolles*. 1997 <https://www.eyrolles.com/Sciences/Livre/Cardiologie-et-pathologie-vasculaire-9782909455679/>. Accessed March 5, 2022.

- [62] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res.* 2014; 114 (12): 1852–1866.
- [63] Louis AJ. Atherosclerosis. *Nature.* 2000; 407 (6801): 233–241.
- [64] Palinski W, Napoli C. The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. *FASEB J.* 2002; 16 (11): 1348–1360.
- [65] Mathur KS, Kashyap SK, Kumar V. Correlation of the extent and severity of atherosclerosis in the coronary and cerebral arteries. *Traffic.* 1963; 27: 929–934.
- [66] Trpkovic A, Resanovic I, Stanimirovic J, Radak D, Mousa SA, Cenic-Milosevic D, et al. Oxidized low-density lipoprotein as a biomarker of cardiovascular diseases. *Crit Rev Clin Lab Sci.* 2015; 52 (2): 70–85.
- [67] Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Traffic.* 2011; 123 (20): 2292–2333.
- [68] Paul JL, Baudin B. Pathophysiology of atherosclerosis and early markers. *Francophone Journal Of Laboratories.* 2009; 2009: 41–50.
- [69] Chronobiology Inserm, Science for health. Inserm. <https://www.inserm.fr/dossier/chronobiologie/>. Accessed March 5, 2022.
- [70] Sánchez A, Calpena AC, Clares B. Evaluating the Oxidative Stress in Inflammation: Role of Melatonin. *Int J Mol Sci.* 2015; 16 (8): 16981–17004.
- [71] de Jaeger C. Physiologie du vieillissement. EMC - Kinésithérapie-Médecine physique-Réadaptation 2018; 14 (1): 1-11.
- [72] Cottart. biology of aging and arteriosclerosis. 2009; 3: 22.
- [73] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Traffic.* 2018; 137 (12): e67–e492.
- [74] Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. *N Engl J Med.* 1994; 330 (20): 1431–1438.
- [75] Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension.* 1989; 13 (6 Pt 2): 968–972.
- [76] Edward. Back To Physio: The blood pressure curve. 2016; 10.
- [77] Lehoux S, Castier Y, Tedgui A. Molecular mechanisms of the vascular responses to haemodynamic forces. *J Intern Med.* 2006; 259 (4): 381–392.
- [78] Califano JP, Reinhart-King CA. Exogenous and endogenous force regulation of endothelial cell behavior. *J Biomech.* 2010; 43 (1): 79–86.
- [79] Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W, Richardson M, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Traffic.* 1992; 85 (1): 391–405.
- [80] Humphrey JD. Mechanisms of arterial remodeling in hypertension: coupled roles of wall shear and intramural stress. *Hypertension.* 2008; 52 (2): 195–200.
- [81] Glagov S. Intimal hyperplasia, vascular modeling, and the restenosis problem. *Traffic.* 1994; 89 (6): 2888–2891.
- [82] Zarins CK, Zatina MA, Giddens DP, Ku DN, Glagov S. Shear stress regulation of artery lumen diameter in experimental atherogenesis. *J Vasc Surg.* 1987; 5 (3): 413–420.
- [83] Cummins PM, von Offenberg Sweeney N, Killeen MT, Birney YA, Redmond EM, Cahill PA. Cyclic strain-mediated matrix metalloproteinase regulation within the vascularendothelium: a force to be reckoned with. *Am J Physiol Heart Circ Physiol.* 2007; 292 (1): H28–42.
- [84] Iba T, Sumpio BE. Morphological response of human endothelial cells subjected to cyclic strain in vitro. *Microvasc Res.* 1991; 42 (3): 245–254.
- [85] Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiol Rev.* 2011; 91 (1): 327–387.
- [86] Samady H, Eshtehardi P, McDaniel MC, Suo J, Dhawan SS, Maynard C, et al. Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. *Traffic.* 2011; 124 (7): 779–788.
- [87] Fukumoto Y, Hiro T, Fujii T, Hashimoto G, Fujimura T, Yamada J, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. *J Am Coll Cardiol.* 2008; 51 (6): 645–650.
- [88] White SJ, Hayes EM, Lehoux S, Jeremy JY, Horrevoets AJG, Newby AC. Characterization of the differential response of endothelial cells exposed to normal and elevated laminar shear stress. *J Cell Physiol.* 2011; 226 (11): 2841–2848.
- [89] Slager CJ, Wentzel JJ, Gijzen FJH, Thury A, van der Wal AC, Schaer JA, et al. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. *Nat Clin Pract Cardiovascular Med.* 2005; 2 (9): 456–464.
- [90] Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. *Traffic.* 2012; 126 (2): 172–181.
- [91] Loscalzo J, Libby P, Epstein JA. Basic Biology of the Cardiovascular System. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, editors. *Harrison's Principles of Internal Medicine.* 2014. New York, NY. McGraw-Hill Education accessmedicine.mhmedical.com/content.aspx?aid=1120804333. Accessed March 5, 2022.
- [92] Chistiakov DA, Orekhov AN, Bobryshev YV. Effects of shear stress on endothelial cells: go with the flow. *Acta Physiol (Oxf).* 2017; 219 (2): 382–408.
- [93] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol.* 2007; 49 (25): 2379–2393.

- [94] Ginsberg HN. Lipoprotein physiology. *Endocrinol Metab Clin North Am*. 1998; 27 (3): 503–519.
- [95] Kolodgie FD, Burke AP, Nakazawa G, Virmani R. Is pathologic intimal thickening the key to understanding early plaque progression in human atherosclerotic disease? *Arterioscler Thromb Vasc Biol*. 2007; 27 (5): 986–989.
- [96] Kolodgie FD, Burke AP, Wight TN, Virmani R. The accumulation of specific types of proteoglycans in eroded plaques: a role in coronary thrombosis in the absence of rupture. *Curr Opin Lipidol*. 2004; 15 (5): 575–582.
- [97] Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012; 32 (9): 2045–2051.
- [98] Mi C, Ma G. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science (New York, NY)*. 1991; 251 (4995). doi: 10.1126/science.1990440.
- [99] Nakashima Y, Wight T, Sueishi K. Early atherosclerosis in humans: role of diffuse intimal thickening and extracellular matrix proteoglycans. *Cardiovascularresearch*. 2008; 79 (1). doi: 10.1093/cvr/cvn099.
- [100] Hunt KJ, Sharrett AR, Chambless LE, Folsom AR, Evans GW, Heiss G. Acoustic shadowing on B-mode ultrasound of the carotid artery predicts CHD. *Ultrasound Med Biol*. 2001; 27 (3): 357–365.
- [101] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Traffic*. 2002; 106 (25): 3143–3421.
- [102] Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. 2000; 151 (5): 478–487.
- [103] Chambless L, Heiss G, Folsom A, Rosamond W, Szklo M, Sharrett A, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol*. 1997; 146 (6). doi: 10.1093/oxfordjournals.aje.a009302.
- [104] van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DAM, Witteman JCM. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Traffic*. 2004; 109 (9): 1089–1094.
- [105] Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Traffic*. 2000; 101 (1): E16-22.
- [106] Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E, et al. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. *J Am Soc Echocardiogr*. 2006; 19 (8): 943–954.
- [107] Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Traffic*. 2006; 114 (16): 1761–1791.
- [108] Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract*. 2005; 55 (520): 838–845.
- [109] Lee AJ, Mowbray PI, Lowe GD, Rumley A, Fowkes FG, Allan PL. Blood viscosity and elevated carotid intima-media thickness in men and women: the Edinburgh Artery Study. *Traffic*. 1998; 97 (15): 1467–1473.
- [110] Okeahialam BN, Alonge BA, Pam SD, Puepet FH. Carotid Intima Media Thickness as a Measure of Cardiovascular Disease Burden in Nigerian Africans with Hypertension and Diabetes Mellitus. *Int J Vasc Med*. 2011; 2011: 327171.
- [111] Booth GL, Kapral MK, Fung K, Tu JV. Relationship between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006; 368 (9529): 29–36.
- [112] Sierra C, de la Sierra A. Early detection and management of the high-risk patient with elevated blood pressure. *Vasc Health Risk Manag*. 2008; 4 (2): 289–296.
- [113] Bounhoure JP. Heart failure and kidney failure: a growing problem! 2006; 5.
- [114] Lee CJ, Park S. The role of carotid ultrasound for cardiovascular risk stratification beyond traditional risk factors. *Yonsei Med J*. 2014; 55 (3): 551–557.
- [115] Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011; 365 (3): 213–221.
- [116] Mayosi BM, Somers K. Cardiomyopathy in Africa: heredity versus environment. *Cardiovascular J Afr*. 2007; 18 (3): 175–179.
- [117] Isaza C, de Seigneux S. Proteinuria: physiological reminder and practical applications. 7.