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Atherosclerosis: What Are We Looking For?

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The subendothelial accumulation of low-density lipoprotein cholesterol (LDL-C) does not occur uniformly across arteries. Instead, LDL-C follows a regional pattern of distribution with areas of low endothelial shear stress (ESS) being the major gateways that allow LDL-C to enter the arterial endothelium.[1,2] The amount of LDL-C that accumulates in the arterial wall is also dependent on the circulating high-density lipoprotein cholesterol (HDL-C) and triglycerides. High-density lipoprotein cholesterol mediates the removal of LDL-C from vascular wall,[3] whereas triglycerides, which are transporters of cholesterol esters to the arterial wall, are linked with decreased HDL-C and increased very low-density lipoprotein (VLDL) cholesterol, a factor that promotes atherosclerosis even in individuals with low LDL-C.[3,4] In cases of increased amounts of LDL-C circulating in the blood, the excessive amount of LDL-C stagnates close to the arterial areas with low ESS and subsequently accumulates in the subendothelial layer.[5] After its initial partial oxidation, the excessive amount of LDL-C cannot be used by the arterial wall and undergoes complete oxidation. Oxidized LDL (oxLDL) further accumulates in subendothelial areas where low-wall stress occurs.[6] oxLDL, as well as oxidized VLDL, in turn trigger the inflammatory response in the subendothelial space. Although inflammation occurs locally, over time it may extend within the arterial wall subsequently increasing the amount of inflammatory biomarkers in the circulating blood.[7] The association of circulating markers of inflammation, such as white blood cells, with the natural history of atherosclerosis is not well elucidated. The white blood cells, in particular mononuclear cells, are actively involved in the pathophysiology of atherosclerosis. However, the role of white blood cells in the evolution and vulnerability of individual atherosclerotic plaques remains unknown.[8,9] This issue warrants further research.

The traditional systemic risk factors for atherosclerosis are in constant interplay with local hemodynamic factors (ie, low ESS) determining the natural history of the disease. Interestingly, in the setting of the same severity of systemic predisposing factors of atherosclerosis, especially hyperlipidemia, greater deposits of oxLDL will occur in coronary arteries with greater curvatures compared to less curved ones. Apparently, it is the local factor of low ESS, which occurs in highly curved areas, that determines the localization and severity of atherosclerosis.[10]

Studies have shown that in the coronary arteries, ESS attains a low and oscillatory pattern during systole, whereas in diastole, it exhibits an initial steep increment up to its diastolic maximum and then it slowly declines throughout the rest of diastolic phase until the closure of mitral valve and the initiation of the next systole.[11,12] Of note, these ESS differences throughout the cardiac cycle are more evident in the curved regions of coronary network. Given the involvement of low and oscillatory ESS in atherosclerosis, one could speculate that the systolic period favors the pathophysiological processes responsible for the onset and development of atherosclerosis, whereas the steep increase of ESS, appearing in diastole, modulates an atheroprotective milieu, compensating for the atherogenic systolic ESS values. Under resting conditions (ie, 60-80 beats/min), the diastole versus systole duration ratio is approximately 2:1; as diastole lasts longer than systole, it compensates for the systolic low ESS values. However, as the heart rate increases, the diastolic time gradually decreases, resulting in an increase of the total time spent on systoles per minute relatively to diastole; of note, in severe tachycardia, the duration of diastole tends to become equal to that of systole. As a result, in regions susceptible to atherosclerosis, the atheroprotective effect of diastole is limited, exposing the endothelium to the atherogenic effect of low- and oscillatory-ESS for longer periods. Therefore, in individuals exposed to the same systemic risk factors for atherosclerosis, the risk of subendothelial accumulation of LDL-C and subsequent atherosclerosis is greater in those with higher number of cardiac pulses. The interplay between heart rate and inflammation is investigated in the article by Inoue et al in this issue of *Angiology*.[13] The authors used the white

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blood cell count as a surrogate marker of subclinical inflammation and found that resting heart rate is positively associated with subclinical inflammation and potentially future cardiovascular events.

The abovementioned concepts regarding the detrimental effect of high heart rate on atherosclerosis could provide a reasonable explanation of the beneficial effect of heart rate-lowering agents, in particular β-blockers, in life expectancy after myocardial infarction, suggesting that the intensive reduction of heart rate could decelerate the progression of atherosclerosis through prolongation of the atheroprotective diastolic phase.[11] The implication of high heart rate in atherosclerosis also indicates the need to redefine the spectrum of normal resting heart rate to 60 to 80 beats/min.[11] This range of cardiac frequency can secure adequate blood perfusion of the coronary arteries, without favoring the development of atherosclerosis.

One could consider atherosclerosis as a physical reaction to excessive accumulation of oxLDL in certain areas within the arterial wall. The subsequent local inflammatory response can be sustained forever, as long as the accumulation of oxLDL is ongoing. Although the assessment of systemic biomarkers of inflammation could help us to understand the pathophysiology of atherosclerosis, one should take into account that this systemic approach has 2 major drawbacks. (*i*) It does not provide information about the localization of atherosclerotic lesions and (*ii*) several other concomitant conditions, which may also contribute to inflammation, could potentially prevent us from attributing the inflammation to atherosclerosis exclusively.

The natural history of atherosclerosis is long lasting and usually asymptomatic provided that the atherosclerotic plaque is not obstructive. However, acute rupture and/or denudation of a given atherosclerotic plaque can occur abruptly any time during the natural history of a given plaque and may provoke immediate aggregation of platelets and activation of the coagulation cascade, resulting in the formation of local obstructive thrombus and precipitation of an acute coronary syndrome. Acute disruption of an atherosclerotic plaque is associated with rapid and greater accumulation of oxLDL in the subendothelial layer, resulting in accelerated progression of atherosclerosis in a relatively short period of time that ultimately leads to the formation of a vulnerable plaque, which is prone to rupture under the influence of local and systematic conditions.[6] Major determinants of plaque vulnerability include fibrous cap thinning, intense local accumulation of inflammatory cells, increased necrotic lipid core, rupture of vasa vasorum within the plaque, which may provoke an abrupt expansion of the lipid core,[14] shift of the balance between proteolytic matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases toward proteolysis,[15] and regional differences of vascular wall stiffness.[16,17] Further to the role of these factors in the pathobiology of plaque vulnerability, one should also acknowledge several conditions that may trigger plaque rupture, such as high ESS, which can lead to abrupt endothelial denudation,[18] intense flow pulsation,[12] and increased heart rate,[11] which may further intensify the local proatherogenic environment. Following plaque rupture, circulating platelets are activated and aggregated, leading to acute clot formation and subsequent precipitation of an acute coronary syndrome.[19]

It should be mentioned that arterial geometry and local hemodynamic factors play a crucial role in the natural history of atherosclerosis, as through mechanotransduction mechanisms, they mediate a complex network of molecular and cellular response.[20]

In summary, atherosclerosis is a physical and chronic inflammatory response to excessive accumulation of oxidized substances (mostly LDL) in the subendothelial space. Over its natural history, atherosclerosis may evolve to vulnerable plaque formation and precipitation of an acute coronary syndrome.

Future research should focus on the prevention of the accumulation of oxLDL in the arterial wall, early detection of vulnerable plaques, further investigation of the specific factors that promote plaque rupture, and development of therapeutic strategies aiming to reduce the potential of vulnerable plaque formation and rupture.

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