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Screening for subclinical atherosclerosis by noninvasive methods in asymptomatic patients with risk factors

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Abstract: Atherosclerosis is a leading cause of cardiovascular death due to the increasing prevalence of the disease and the impact of risk factors such as diabetes, obesity or smoking. Sudden cardiac death is the primary consequence of coronary artery disease in 50% of men and 64% of women. Currently the only available strategy to reduce mortality in the at-risk population is primary prevention; the target population must receive screening for atherosclerosis. The value of screening for subclinical atherosclerosis is still relevant, it has become standard clinical practice with the emergence of new noninvasive techniques (radio frequency [RF] measurement of intima-media thickness [RFQIMT] and arterial stiffness [RFQAS], and flow-mediated vasodilatation [FMV]), which have been used by our team since 2007 and are based on detection marker integrators which reflect the deleterious effect of risk factors on arterial remodeling before the onset of clinical events. These techniques allow the study of values according to age and diagnosis of the pathological value, the thickness of the intima media (RFQIMT), the speed of the pulse wave (RFQAS), and the degree of endothelial dysfunction (FMV). This screening is justified in asymptomatic patients with cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, and tobacco smoking). Studies conducted by RF coupled with two-dimensional echo since 2007 have led to a more detailed analysis of the state of the arterial wall. The various examinations allow an assessment of the degree of subclinical atherosclerosis and its impact on arterial remodeling and endothelial function. The use of noninvasive imaging in screening and early detection of subclinical atherosclerosis is reliable and reproducible and allows us to assess the susceptibility of our patients with risk factors and ensures better monitoring of atherosclerosis, thus reducing the occurrence of cardiovascular events in the long term.

Keywords: radio frequency, RF QIMT, RF QAS, FMV, arterial age, velocimetry, MRI

Introduction

Atherosclerosis is considered a chronic inflammatory disease related to age, having a long, slow asymptomatic phase. Recent data show that it begins to develop early in life and manifests itself clinically in many patients at a relatively advanced stage. The consequences of atherosclerosis, responsible for cardiovascular diseases, are among the leading causes of morbidity and mortality in the world. It should also be noted that coronary heart disease due to atherosclerosis is increasing. Diagnosis and treatment are a priority, partly because sudden death is the primary consequence of coronary artery disease in 50% of men and 64% of women.[1] Early detection of atherosclerosis has become possible due to new noninvasive imaging techniques

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for patients with risk factors, allowing us to detect subclinical atherosclerosis and minimal changes or damage to the vascular walls, which can be potentially corrected by receiving preventive treatment.

At present, the evaluation of arterial status is possible since the advent of new techniques. These are techniques that allow the study of arterial status and its physiological or pathological remodeling (geometric or functional). In addition, these new techniques are very promising for detecting subclinical atheroma and the degree of infiltration of the arterial wall by measuring the intima-media thickness (IMT),[2] arterial stiffness (AS),[3] and the echo particle image velocimetry (EPIV)[4] used in the calculation of the constraint of the carotid wall and of the level of endothelial dysfunction by the flow-mediated vasodilation (FMV)[5] method.[1–3,25,40]

To complete the screening protocol,[6–8] in a few years we will have specific biomarkers directly related to the progression of atherosclerosis (the study of metalloproteases or bioprotease obtained from a sample of urine, or of plasma to be systematically associated with previous methods), so as to refine the results by the end of testing and guide our future treatment decisions. At the moment, these specific biomarkers remain in the research stage. Moreover, all biomarkers currently used in the assessment of cardiovascular risk are low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), ultra-sensitive C-reactive protein (us-CRP), glycated hemoglobin, creatinine clearance, von Willebrand factor, myeloperoxidases, cytokines, and other markers of platelet reactivity.[9] Markers of both oxidative stress[10] and calcium score[11] (calculated by coronary computed tomography) are useful in the current screening but unfortunately are not specific in the diagnosis of subclinical atherosclerosis.

The use of new noninvasive imaging techniques in the detection of subclinical atherosclerosis could become a screening panel of reliable and reproducible detection for use in daily practice in asymptomatic patients with risk factors, so as to stratify the risk and reclassify it upward to provide targeted support for patients and develop appropriate preventive measures aimed at reducing the occurrence of cardiovascular events, which are the main vascular targets in public health in the 21st century. Toward that end, the objective of this research is to promote the screening and early detection of subclinical atherosclerosis in asymptomatic patients with cardiovascular risk factors via mass screening or individual screening.[12]

Cardiovascular risk factors

Cardiovascular risk factors (CVRFs) are modifiable parameters associated with the occurrence of a cardiovascular event that increase the probability of this event: hypertension increases the probability of death by 13%,[13,14] tobacco by 9%,[15–18] dyslipidemia by 8% with its atherogenic effect, and by 7% malnutrition, as well as increasing the incidence of diabetes, obesity, and high body mass index, except where age remains the only nonmodifiable risk factor.[19,20] Known CVRFs such as hypertension,[29] smoking, and diabetes were included in multiple models to assess the risk of a cardiovascular event occurring in the general population. This concept of an overall estimate of risk can predict cardiovascular risk, which plays a key role in individualized therapeutic measures.[21,22]

Cardiovascular intermediate markers

Cardiovascular integrator markers are quantifiable parameters reflecting the deleterious state caused by risk factors and are linked to the occurrence of clinical events. Integrator markers are universal and are the bridge between risk factors and the occurrence of a cardiovascular event, for which they are directly responsible.[23,24]

Atherogenesis

The origin of atherosclerosis begins in childhood and evolves in bouts of the disease with lesions of an inflammatory character. Through this inflammation, atheromatosis transforms a localized disease into a generalized illness. The main lesion is the atheroma plaque, which is part of the genesis of the first modifications in the arterial wall – that is to say, microcirculatory disturbances all the way to endothelial dysfunction.[25–27]

Genetic factors

Atherosclerosis is a multifactor disease of which approximately 40% of cases are attributed to genetic factors and 60% to environmental factors. Many ongoing projects are underway on the importance of single nucleotide polymorphisms,

Table 1 QIMT: IMT results according to age, Study of Athis Mons

Age (years)	IMT (μm)	IMT average (μm)
20–30	170–310	240
30–39	320–390	35
40–49	400–490	450
50–59	500–590	545
60–69	600–700	650

Note: Pathological values: IMT > 900 microns (0.9 mm).
Abbreviations: IMT, intima-media thickness; QIMT, measurement of IMT.

Table 2 QAS pulse wave velocity according to age, Study of Athis Mons

Age (years)	PWV average speed (m/s)	Speed range (m/s)
20–30	4.5	2.5–5.7
30–39	6.5	5.9–7.3
40–49	8.0	7.5–8.5
50–59	9.0	8.6–9.4
60–69	10.4	9.7–11.1

Notes: PWV values (male/female) were based on age.[48] The QAS and QIMT are currently used in the early detection of subclinical atherosclerosis and must be systematically associated with the FMV at the humeral artery to assess the degree of endothelial dysfunction.
Abbreviations: FMV, flow-mediated vasodilatation; PWV, pulse wave velocity; QAS, measurement of arterial stiffness; QIMT, measurement of intima-media thickness.

and approximately 150 genetic markers located on 80 genes showing an association with coronary artery disease have been cataloged. Of these, 10 have been proposed to improve the prediction of cardiovascular risk.[27,28] Through the development of DNA microarrays, it is now possible to detect 500,000 different polymorphisms in a single trial. These techniques are likely to identify genetic variants capable of bringing forward the prediction of cardiovascular risk further than known risk factors alone.[29–32]

Associated factors

The existence of several theories on atherosclerosis demonstrates a set of associated factors apart from a detailed lipid and total cholesterol profile (TC-LDL-HDL-TG): changes in blood glucose levels, postmenopausal status (elevated CRP, us-CRP), fibrinogen (in men), left ventricular mass, male sex, advanced age, systolic blood pressure, smoking, body mass index, diameter of the waist, low physical activity, family history, and alcohol.[33–37]

Etiology of inflammation

Oxidative stress

Oxidative stress is the principal etiology and the beginning of the alteration of the arterial wall. It can be defined as an imbalance in the body between the biological levels of antioxidants and free radicals, or between the enzymatic systems of oxygen and free radicals. This imbalance causes side effects by decreasing the bioavailability of nitric oxide (NO), arginine, and adenosine triphosphate, a destructive cascade identified at the arterial wall, followed by the initiation of chronic inflammation, leading to a disruption of the protective functions of the endothelium. The dysfunction of protective mechanisms against atherosclerosis leads to vascular dysfunction and the progressive onset from subclinical lesions to clinical pathological manifestations. Causes that promote oxidative stress are hypoxia, respiratory diseases exacerbated by repeated pulmonary infections, smoking, frequent exposure to the sun, alcohol, and air pollution.[38–42]

Role of the renin angiotensin system

The renin angiotensin system participates in the remodeling of the arterial wall. Stimulation of the angiotensin II AT1 receptor increases cell adhesion, which allows monocytes to infiltrate the endothelium. Here they transform into macrophages, which then accumulate and become foam cells. These cells secrete cytokines and inflammatory markers (interleukins, CRP) follow the assault.[33] The inflammatory response alters the arterial wall. The first manifestation of this infrastructural disease remodeling is a disruption of elastic blades of the intima media, along with the migration of smooth muscle cells to the subendothelial space, which transforms into fibrocytes or myofibrocytes.[43–46]

Chronic inflammation

Chronic inflammation is a result of the major consequences of oxidative stress and renin angiotensin system imbalance associated with the deleterious effect of known risk factors that lead to the alteration of the arterial wall. Inflammation plays a key role in all stages of the formation of vascular lesions maintained and exacerbated by risk factors. Chronic inflammation results in changes in the arterial wall, such as geometric vascular remodeling (the increase in IMT) and functional remodeling. The consequence of chronic inflammation is endothelial dysfunction, which sets in and can be defined as an integrated marker of the damage to arterial walls by classic risk factors.[47]

Study techniques of intermediate markers

Which technique and what method? Since 2007, noninvasive imaging has been used in the diagnosis of subclinical atherosclerosis, as well as the detailed analysis and more precise calculation of the IMT, the velocity of the pulse wave (PWV), and the degree of endothelial dysfunction at the level of the brachial artery by the FMV method. At present, the techniques and methods used are as follows:

- QIMT: This is the measurement of IMT in the carotid artery – the study of geometric remodeling of the artery (Table 1).
- QAS: This is the study of AS in the carotid artery, measuring the speed of the pulse wave and alpha and beta stiffness parameters – the study of the functional remodeling of the artery (Table 2).

- FMV method: FMV is a complementary method used to assess the degree of endothelial dysfunction in patients with risk factors and their repercussions at the level of the endothelium. The examination is of the brachial artery – the study of the variation of the mean diameter of the artery and postreactive hyperemia relative to the baseline diameter.

Conducting reviews

QIMT

The thickening of the intima media in the development of atherosclerosis shares the same pathophysiological mechanisms in development and progression. The physiological progression of IMT is 1–5 microns per year. The increased or pathological IMT is a high-risk marker both for independent and predictor cardiovascular events. IMT etiology increase is linked to hypertension, diabetes, smoking, high body mass index, and dyslipidemia. The main objective of this method is the detection of infraclinical atheroma in the earliest phases in patients with risk factors, but it is also useful in monitoring the progression of IMT in patients with poorly controlled risk factors, such as diet and lifestyle factors or with unsupervised drug treatments. When the IMT is pathological, the risk of stroke and myocardial infarction is predictable. The screening and detection of subclinical atherosclerosis will allow us to achieve specialized care and reduce the frequency of occurrence of cardiovascular events. Completion of the review and technical review of the method was made in accordance with the IMT Mannheim protocol (Mannheim consensus initiated in 2004 and again in 2006).[48,49]

QAS

AS is an independent marker predictive of cardiovascular events. The review aims to make early detection of functional remodeling of the artery in patients with risk factors, through the study of the PWV and the parameters of the α and β rigidity. In this technique, we study the PWV. This allows us to detect early patients with high-speed PWV relative to their age bracket, reflecting early atherosclerotic impregnation occurring before the diagnosis of stiffness according to the value published in various pathological studies (12 m/s) is confirmed.

PWV measurement is used to evaluate AS in real time. This measure is intended to assess the degree of aging of the arterial system and its influence on the central pressure and pulse (clinical markers). The QAS used in our study is a reliable and reproducible technique that allows us to achieve real-time calculation of the PWV dimension parameters of stiffness coefficients (α, β) at the carotid level. The pathological threshold of different parameters used by this method of study are the PWV – VOP $\leq$ 12 m/s (age limit 70 years) and the size of the coefficient stiffness parameters (α, β): $\alpha \geq 11$ and $\beta \geq 20$.

The measurement technique is first carried out on the scouting ultrasound common carotid artery with a 7.5 MHz transducer in two-dimensional (2D) mode. The measuring window is placed with the line 1 cm from the bulb, with three alternating 15-mm measurements taken on each common carotid. Color indicators should be parallel to the artery walls, remaining synchronous to the kinetics of said walls. The curve of the PWV must be smooth and morphologically regular and analyzed for 10–12 seconds. The process stops at the moment the standard deviation (SD) is <5. The resulting figure distension, called a "spontaneous shutdown procedure," is used to calculate the coefficients of the dimensions of the stiffness parameters.

FMV

FMV is an additional technical noninvasive, reproducible, inexpensive method used in the indirect assessment of the degree of endothelial dysfunction, directed at the brachial artery and applicable to patients with risk factors. The analysis of the pathological results is correlated with the progression of infra-clinical atherosclerosis. This growth will be compounded by the degree of oxidative stress and severity of risk factors or poor control of the disease.[5,50–52]

Methods

The measurement technique is based on initial ultrasound detection (with a 7.5 MHz linear transducer in 2D mode) of the humeral artery above the arm's antecubital fossa, followed by radio frequency measurement of the mean diameter and spectral analysis of the baseline blood flow (in cm/second). Once these baseline measurements have been made, an inflatable cuff (with a defined length of 10 cm) is placed around the proximal third of the arm and a 300 mmHg occlusive pressure is applied for 5 minutes. The first step is to then measure the baseline brachial artery diameter and flow. The next step is to measure the brachial artery diameter and flow after reactive hyperemia. In case of pathology, a physiological 15-minute arterial recovery period is required before continuing to the second part of the procedure (only in patients presenting endothelial dysfunction diagnosed by radio frequency (FMV)).

The second part of the procedure is the reversibility test, which is used to assess endothelial function (FMV). While NO

donors were used, we tested the reversibility of the endothelial dysfunction, as well as the additional effect of cyclic monophosphate on the healthy endothelium. The reversibility test with an FMV-NO donor is expressed as the percentage recovery of the arterial diameter after reactive hyperemia compared to the same artery's baseline diameter.[45,47,50,51–54] In addition to these new technical noninvasive tests for the detection of subclinical atherosclerosis, two new tests have recently emerged, with very encouraging results: echo particle image velocimetry (EPIV) and magnetic resonance imaging (MRI) velocimetry.[53–55]

EPIV

EPIV is a new technique in the detection of subclinical atherosclerosis, used in measurements of shear wall stress through vector analysis of blood flow velocities of the wall at the carotid bifurcation. It has a technical high-temporal resolution of 0.7 ms and a spatial resolution of 0.4 mm, combining EPIV contrast with a conventional 2D echo method. This technique is a synthesis of two technologies: particle image velocimetry and brightness mode ultrasound contrast. The most recent development of micro-bubbles improved imaging based on ultrasonic velocimetry of vascular flow. The parameters analyzed are the vascular speed profile, velocity vector, speed, maps, and hemodynamic blood flow to the wall shear stress (calculating the average shear stress in the arterial wall in dyne/cm²). The contrast agent used is a product of contrast micro-bubbles, which allows a better study of velocities and stresses. The standards used for the wall stress are $-20 + 5$ dyne/cm² and wall pathological stress > 200 dyne/cm².[56–59]

MRI velocimetry

MRI velocimetry is a very promising technique for the detection of subclinical atherosclerosis. This technique studies the velocity profile, shear rate, and general flow stress of the wall. It is a noninvasive technique, more sensitive and reliable than the EPIV (with the border error between the two techniques of 10% for MRI). The problem now is that it is not routinely used, and it is not always available on a daily basis. MRI velocimetry has both advantages and disadvantages, due to its high temporal resolution; it is now considered a promising approach for the noninvasive assessment of changes in carotid wall thickness, a marker for subclinical atherosclerosis in young patients with high risk and abdominal adiposity.[60–63]

Biomarkers

A biomarker is a characteristic objectively measured with sufficient accuracy and reproducibility and evaluated as an indicator of pathological or physiological processes, or as the effect of a drug. At present, most of these biomarkers are used in research, with multiple studies in progress to identify the precise profiles of subjects who could benefit from dosages of these biomarkers. However, some biomarkers we studied open up interesting prospects and play an important role in the study and progression of atherosclerosis.

The presence of high levels of these biomarkers greatly increases the risk of developing cardiovascular disease in healthy subjects with risk factors, or in patients at high risk. If these results are confirmed, it would be possible in the future to identify people at risk for cardiovascular disease and its complications and offer them appropriate treatment. Currently, these biomarkers are still in the research stage with multiple ongoing studies to identify the precise profile of subjects who may benefit from dosage by these biomarkers. The use of biomarkers should be used in asymptomatic patients with risk factors, associated with previously described techniques, for better stratification of risk and the reclassification of patients from intermediate to a higher cardiovascular risk.[64]

In the future, annual control specific biomarkers in patients with risk factors who had a management target will be systematic.[65–69] An improvement or normalization of biomarkers translates to a significant decrease in the progression of atherosclerosis. This protocol assessment of the arterial age will be associated with protocols Framingham and European System for Cardiac Operative Risk Evaluation (EuroSCORE) and to assess the real risk in patients with cardiovascular risk factors.[70–73]

In the future, monitoring of specific biomarkers once a year should be undertaken in patients with increased values of parameters measured with noninvasive techniques. After standardization, the use of these new techniques will support targeted and good control of risk factors, reflected by a decrease in the progression of atherosclerosis and cardiovascular diseases.

Conclusion

Traditional risk factors predict future cardiovascular events and are major determinants in the assessment of cardiovascular risk (Framingham score[74,75] and EuroSCORE[76–79]) and the choice of primary prevention strategy. Despite the undeniable progress made in the diagnosis of cardiovascular disease, and especially its management along with a decrease in mortality, cardiovascular disease remains a major cause of morbidity and mortality in Western countries, partly because sudden death is the first evidence of coronary artery disease in 50% of men and 64% of women. In future years, it is feared that there will

be a further increase in the prevalence of cardiovascular disease secondary to the aging population and the rise in obesity and diabetes. Currently the only available strategy to reduce mortality in this population is primary prevention – atherosclerosis screening of the target population. This approach in primary prevention is more effective when it is directed toward the early detection of subclinical atherosclerosis using new noninvasive imaging techniques that add value, not only in the screening of asymptomatic patients with risk factors, but also in the stratification of cardiovascular risk and greater upward reclassification for patients at intermediate risk so that they can receive preventive treatment with targeted support tailored to each patient, thus enabling them to avoid the occurrence of a cardiovascular event in the short and medium term. These new techniques (QIMT, QAS, and FMV) allow us to have an overall picture of the state of physiological or pathological arterial remodeling and the degree of endothelial dysfunction. The results obtained with these techniques in the future will be associated with specific biomarkers to refine the diagnosis of subclinical atherosclerosis.[80–84]

These abnormal or pathological results significantly increase the amount of predictive information provided by traditional risk factors. The descriptions above show that the three noninvasive imaging tests (QIMT, QAS, and FMV) are promising technologies. These techniques are reliable, reproducible, and inexpensive, and we believe in the near future that doctors will have new intermediate markers to evaluate early subclinical changes in the arterial wall and will introduce them into their clinical assessments and in the monitoring of patients.[85–95]

Disclosure

The authors report no conflicts of interest in this work.

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