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MARKERS OF SUBCLINICAL VASCULAR LESION IN IMAGING: WHEN AND WHY TO REQUEST THEM

MARCADORES DE LESÃO VASCULAR SUBCLÍNICA EM IMAGEM: QUANDO E PORQUE SOLICITÁ-LOS

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ABSTRACT

Atherosclerotic disease is a slowly progressive condition, thereby providing the opportunity to intervene in the patient's lifestyle, and even pharmacologically, in an attempt to increase event-free life expectancy. To this end, risk stratification models based on classic criteria such as the Framingham criteria are generally used to stratify the individual patient risk, but there is a considerable number of events that occur in cases considered low risk. The main uncertainty arises in cases considered intermediate risk, and in these situations, imaging tests can help identify and appropriately treat cases of greater severity. The assessments are generally performed using carotid artery ultrasound and the measurement of calcium score by computed tomography, with each method having its own particularities and technical limitations. The performance of the methods largely depends on the available equipment and the expertise of the medical staff involved. However, there are clear advantages of plaque research in carotid arteries (ACA) and of the quantification of calcification in the carotid arteries (CAC) over the evaluation of intima - medial thickness (IMT), while investigation of the degree of coronary calcification is recommended in recent international guidelines. Meanwhile, questions remain as to whether the techniques perform differently in the risk stratification of infarction and stroke.

Keywords: Atherosclerosis; Carotid Intima - Medial Thickness; Carotid Arteries; Plaque, Atherosclerotic.

RESUMO

A doença aterosclerótica tem evolução lenta, o que dá a oportunidade de intervir no estilo de vida e até farmacologicamente na tentativa de aumentar a expectativa de vida livre de eventos. Para esse fim, habitualmente utilizam-se modelos de estratificação de risco baseada em modelos clássicos, como os critérios de Framingham, mas há um número representativo de eventos que acontecem em casos considerados de baixo risco. As principais dúvidas surgem nos casos considerados de risco intermediário, e, nessa situação, os exames de imagem podem auxiliar a identificar e tratar adequadamente casos de maior gravidade. Habitualmente, as avaliações são feitas por ultrassom das artérias carótidas (ACa) e pela medida do escore de cálcio por tomografia, cada um com suas particularidades e limitações técnicas. O desempenho dos métodos depende, em grande parte, do equipamento disponível e da expertise da equipe médica envolvida. Contudo, há claras vantagens da pesquisa de placas nas ACa e da quantificação da calcificação nas artérias carótidas (CAC) sobre a avaliação da espessura médio intimal (IMT - do inglês intima-media thickness), enquanto a pesquisa do grau de calcificação coronariana é recomendada em recentes diretrizes internacionais. Ao mesmo tempo, persistem algumas dúvidas se os exames têm desempenho distinto na estratificação de risco de infarto e acidente vascular cerebral.

Descritores: *Aterosclerose; Espessura Íntima-Média Carótida; Artérias Carótidas; Placa Aterosclerótica.*

INTRODUCTION

The identification of atherosclerotic disease in its subclinical phase is preferred to promote lifestyle changes and enable the early initiation of pharmacological treatment to reduce adverse outcomes. To this end, clinical and laboratory risk factors are often analyzed and patients are classified as low, moderate, or high risk. Nevertheless, there is a significant discrepancy between the conventional risk assessment and the incidence of adverse coronary events; thus, myocardial infarction (AMI) and stroke are commonly found in intermediate-risk patients.[1-3] As a result, undesirable consequences are observed due to excessive treatment in low-risk individuals or not treating more aggressively those patients who present with atheroma plaques and, consequently, are at higher risk.[2,3]

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Therefore, there is great potential for the use of non-invasive imaging methods that can show the presence of atheroma plaques, thus indicating which cases are at higher risk of adverse events (AE) and effectively require pharmacological treatment to decrease events and increase patient survival. Herein, we review the diagnostic methods that have been proven useful and can contribute to clinical practice.

ASSESSMENT OF MEAN INTIMA-MEDIA THICKNESS OF CAROTID ARTERIES

Atherosclerosis usually compromises different arterial territories, among them the carotid arteries (CA), which in turn can be easily assessed using ultrasonography since they are superficial vessels and, therefore, can be reached using this propaedeutic.[4] Thus, the early identification of atherosclerosis in these vessels could be used to effectively identify which patients would benefit from more intense treatment.[4] With the objective of diagnosing atherosclerotic disease before the occurrence of cardiovascular events (CE), early studies measured intima-media thickness (IMT) of the arterial vessel wall. Atherosclerosis can promote changes in the vessel walls for years before the appearance of plaques and clinical manifestations, thus giving the opportunity to positively intervene in the natural history of the disease.[4,5] Ultrasonography is a safe method that does not use ionizing radiation or contrast media and has suitable spatial and temporal resolution characteristics to image the CA, even in motion, and identify normality or the presence of changes in the vascular wall resulting from atherosclerosis, even before the onset of clinical manifestations of the disease (Figure 1).[6]

Different studies showed a correlation between an IMT above 1.0 mm and a higher incidence of CE. The Rotterdam control case study assessed 374 patients with AMI or stroke and compared the IMT of this population with those of 1496 control cases and found that the area under the curve (AUC) was 0.71; upon the consideration of conventional risk factors, it was 0.65.[7] The combination of the clinical and imaging data revealed an AUC of 0.72 (95% confidence interval [CI], 0.69–0.75).[7] Later, the Cardiovascular Health Study Collaborative Research Group assessed 5858 patients aged 65 years or older for 6.2 years and found that patients in the higher quintiles had a 3.87 times greater risk of AE (95% CI, 2.72–5.51) than those in the lower quintiles and could predict both the incidence of AMI or stroke and the combined objective of these different outcomes.[4] This study also found that the risk was progressively increased for each quintile of increased thickness of the CA wall with an increased relative risk for both stroke and AMI.[4] A meta-analysis performed by Lorenz et al. analyzed eight different studies that included between 1275 and 14214 patients for 3 to 10.7 years and found that when the ultrasound showed arteries free of atheroma plaques, the clinical evolution was more favorable.[8] Despite some study heterogeneity, the authors suggested that IMT increases were associated with worse prognosis, highlighting the fact that this parameter was more effective at identifying patients at higher risk of adverse cerebrovascular outcomes than coronary events. Furthermore, the authors found that the relationship between the incidence of AE and IMT was not linear, i.e., disease progression was more unfavorable in cases of abnormal thickening of the CA walls. However, they did not increase proportionally to the increase of 0.10 mm in the intima-media layer.[8]

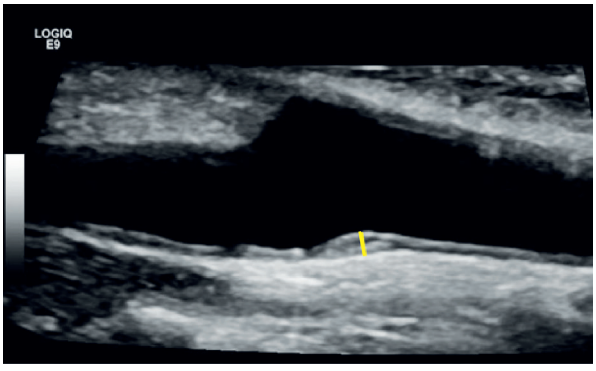

Figure 1. The presence of atherosclerosis promotes several changes in the arterial structure, including increased intima-medial thickness (IMT), that can be assessed by vascular ultrasonography. In this example, the yellow line shows the measurement of a patient with increased IMT equivalent to 1.4 mm (VN < 1.0 mm).

Other studies have suggested that this approach could be useful for reclassifying patients into different subgroups. Cardoso et al. followed 478 Brazilians with type 2 diabetes for 10.8 years and identified worse prognosis when the IMT was between 1.5 and 1.8 times the reference values.[9] Magnussen observed that the greater the IMT in hypertensive individuals, the higher the incidence of CE. However, he drew attention to the fact that defining a value of 0.9 mm as the upper limit of normal might be a conservative measure and highlighted the difficulty of standardizing the acquisition and analysis of images to avoid erroneous conclusions.[10] The potential of this measure in women was reported by Timóteo et al., who found a positive relationship between this IMT and the incidence of AE in 300 cases, stating, however, that the increase was not very expressive (AUC, 0.68; 95% CI, 0.576–0.701, $p < .001$).[11]

Nambi et al. measured IMT in 13145 patients and observed reclassification of risk in 23% of cases, the impact being greater in men than in women. Conversely, they stated that investigating the presence of atheroma plaques in the CA could be a more effective method for risk stratification.[12]

However, other evidence and meta-analyses questioned the real clinical contribution of IMT. A review of studies including a total of 45828 patients showed that the test allowed the adequate reclassification of only 0.8% of the population as at risk of having CE.[13] These inconsistencies may be partially caused by differences in the testing techniques used, as some authors performed measurements in the proximal portions of the CA, others in the distal segments, some trials perform multiple measurements, and others perform a single measurement; other inaccuracies may have impacted the interpretation of the results.[14] Considering that atherosclerosis does not equally compromise the entire extent of the CA but prefers some regions of the vessel, differences in the numbers and locations of measurements may give different impressions on vascular health-inducing errors.[14]

The potential of magnetic resonance imaging (MRI) as an alternative to measuring IMT to improve risk stratification was tested and proven to be a safe method that reproduces the entire arterial territory without the use of ionizing radiation

while better reproducing the carotid anatomy.[15] Initial studies confirmed the ability of this test to accurately identify higher risk cases and assist in the patient reclassification. However, the greater complexity of this test impairs its daily use in the screening for atherosclerotic disease in the subclinical phase for large population groups. However, despite these favorable perspectives, ultrasonography remains the preferred method for this type of analysis.[16]

DIAGNOSIS OF ATHEROMA PLAQUES IN CA

Contrary to what occurs when measuring the IMT of CA, the presence of atheroma plaques in some arterial territory allows the definitive diagnosis of atherosclerosis and the identification of individuals at higher risk of CE with a higher degree of accuracy.[6,17] This approach is simpler to standardize, has less intra- and interobserver variability, and allows patient follow-up over time.[6,17] Furthermore, current ultrasonography techniques enable both the identification of the plaque and the estimation of its area, volume, degree of stenosis, and hemodynamic impact, elements that indicate the severity of the ongoing atherosclerosis process and can provide useful treatment information. Once again, because they are easily accessed, the CA were chosen for this assessment (Figures 2A, 2B). In 2002, Spence et al. analyzed the potential of use of this test in 1686 patients without a previous diagnosis of coronary disease, followed up by 5 years, dividing the cases into quartiles according to the variation of maximum plaque thickness. There was a direct relationship between the evolution and progression or regression of plaque dimensions, with an annual event rate of 9.4% in patients with plaque regression, 7.6% in those without changes in atheroma, and 15.7% in patients whose obstructions progressed ($p = 0.003$).[18] Additional emphasis should be given to the fact that drug intervention was associated with changes in clinical outcomes.[18]

Later, Rundek et al. reviewed the data of 2189 patients from the Northern Manhattan population study, in which carotid ultrasonography was performed and atheroma plaques were found in 1263 patients (58%). At the end of 6.9 years of evolution, 319 patients had AE, with a 2.8 times higher risk in cases with a plaque of 1.9 mm or more. The authors emphasized that the presence of plaques in CA remained the only predictive variable of events in Latino patients, and 44% of patients considered low risk by the Framingham score were considered to have 18.3% chance of developing AE once they had plaques in the CA.[19] This is an important fact because one of the most relevant aspects of a biomarker is its ability of changing the clinical risk classification defined by conventional clinical models. Perez et al. confirmed that investigating atheroma plaques in CA is an effective way to improve risk stratification based on the Framingham criteria.[20] In 2035 Argentine patients, the presence of plaques in CA increased the chance of AE from 51.5% to 61.8% (index $K = 0.360$; $p < 0.05$), and the authors concluded that this parameter should be incorporated into clinical practice.[20]

Gardener et al., when reviewing 1374 patients from the Northern-Manhattan study, showed that the presence of plaques could be used to monitor the effectiveness of therapeutic measures. They showed that moderate or strict adherence to the Mediterranean diet associated with a healthier lifestyle resulted in plaque stability or even regression, thus having a protective effect in the studied population.[21]

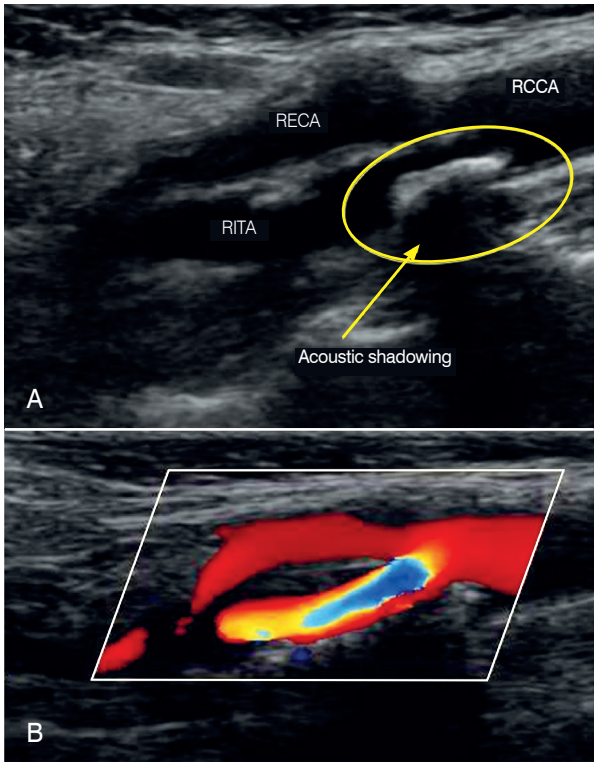

Figure 2. A) Ultrasound allows the diagnosis of atheroma plaques in the carotid arteries, which indicate the presence of systemic atherosclerosis and a higher risk of the occurrence of adverse cardiovascular events. In this example, a calcified plaque defined by the existence of acoustic shadowing (arrow) in the distal portion of the right common carotid artery (RCCA) is present, which also compromises the origin of the right internal carotid artery (RITA) but does not affect the right external carotid artery (RECA). B) In addition to revealing atheroma plaques, ultrasound enables other measurements, such as the impact of stenosis on arterial flow. In this example, color Doppler reveals a significant change in flow due to the presence of stenosis.

The meta-analysis of Ibama et al. proved the superiority of the investigation for atheroma plaques in CA versus IMT measurements.[22] Upon evaluating 27 studies of 4878 patients, they found no significant differences in the diagnosis of obstructive coronary disease, but after reviewing 11 studies including 54,336 patients, they observed the presence of plaques in the CA and the risk of AMI during disease progression was higher than ability to identify cases of higher risk for occurrence of AMI.[22] Upon inclusion of the investigation for atheroma plaques, the AUC increased from 0.61 to 0.64 (95% CI, 1.1–1.82; $p = 0.04$)[22]. This superiority was supported by the results of the Bioimage study, which analyzed 6102 asymptomatic individuals (men aged 55–80 years, women aged 60–80 years).[17] It should be noted that CA imaging was not restricted to a short segment of the cervical territory; it included the entire bilateral path of the CA from the origin to the distal portions of the internal CA. The authors determined the atherosclerotic load from the sum of all segments with plaques along the entire path of the CA bilaterally.[17] The follow-up time of the patients was the shortest among the

above mentioned studies at a mean of 2.7 years, but the atherosclerotic load of CA was effective for reclassifying the patients because the chance ratio of events in individuals without carotid atheromatosis was 0.78 (95% CI, 0.31–1.91); in those with a higher load, it was 2.36 (95% CI, 1.13–4.92). [17]

Thus, the investigation of atheroma plaques in CA using ultrasonography has a proven role in clinical practice by modifying the assessment made by conventional models, reflecting the impact of lifestyle interventions on the clinical evolution of patients and being a safe and easily performed test. Conversely, the assessment of some details of the studies suggests that this parameter has a somewhat greater ability to identify the cases at higher risk of stroke than of CE. However, they agree that the presence of stenosis in CA represents an independent risk factor to identify cases with a worse prognosis.[17-20]

Moreover, MRI was proposed to investigate atheroma plaques in CA; its main feature is the higher contrast resolution that allows better characterization of the atheroma components, which could reflect the progression of atherosclerosis.[23,24] This enthusiasm was confirmed by experimental studies that demonstrated the test's potential to detect plaques in those vessels, quantifying the degree of reduction in the arterial lumen and estimating the hemodynamic impact of the plaque.[23,24] Bissell et al. demonstrated the test's potential to serve as a biomarker, assessing 64 patients not diagnosed with coronary disease or diabetes who underwent CA MRI. Although their results showed an association between the test findings and conventional risk factors, stenosis was observed in some cases not considered high risk by conventional models.[25] Although this study relies on a small sample, it stimulates further research to confirm the potential contribution of resonance imaging. The practical use of the test is limited by its greater complexity than ultrasonography.

SUBCLINICAL DIAGNOSIS OF ATHEROSCLEROSIS FROM CA IMAGING: WHAT TO VALUE

IMT measurements are commonly made and can be performed on any ultrasonography machine. It may be limited by wide intra- and interobserver variability, but this may only be a consequence of the presence of hypertension. No studies to date have reported changes in outcomes as a result of the change in this index. CA plaques, in turn, more accurately reflect the presence of atherosclerosis before clinical manifestation and have a stronger correlation with the incidence of AE. Although its recording may be more complex because the best results are obtained from three-dimensional ultrasound imaging, its clinical contribution is certainly more relevant and enables better individualization of preventive measures. Although tomography and MRI have higher spatial resolution (tomography) and contrast resolution (resonance), the greater complexity of these methods impairs them from being widely used for population screening for subclinical atherosclerosis.[17]

DIRECT IDENTIFICATION OF CORONARY ATHEROSCLEROSIS

The possibility of reporting the presence of atherosclerosis in the coronary arteries arouses great interest because it brings the possibility of improving the risk stratification by identifying patients at higher risk of developing CE. The main objective in these cases is to identify patients who need radical lifestyle changes and even medication to increase event-free life expectancy.

One possibility is assessing the coronary artery calcification index (CAC), whose clinical use started in the last few decades of the 20th century, with performance of electron-beam tomography using equipment that is no longer manufactured but had favorable characteristics including a high temporal resolution and a low dose of radiation. The technology and method were validated by Agatston et al., who found that the results obtained with this technique in the detection of areas of calcification in the coronary arteries were correlated with those obtained by fluoroscopy. The models for interpreting the test and the suggestions made on the impact of its results on clinical practice were standardized in the 20th century.[26,27]

From a practical point of view, the quantification of CA using tomography includes the acquisition of 3-mm-thick transverse images without the use of iodinated contrast medium coupled to the electrocardiogram findings. The analysis is performed in workstations with specific programs to measure the degree of calcification, defined as regions with hyperattenuation of at least 130 Hounsfield units (HU) of attenuation in at least 3 adjacent pixels (1 mm^2) in 3-mm-thick sections. [26-29] The Agatston method also includes the use of a correction factor to compensate for the attenuation that calcium may have caused on the x-rays: Factor 1 is considered in plaques that attenuate between 130 and 199 HU, factor 2 in plaques with HU ranging between 200 and 299 HU, factor 3 when the attenuation ranges between 300 and 399 HU, and factor 4 when the attenuation is above 400 HU.[26-29] Conversely, the result is usually expressed in absolute values with the inclusion of the areas in which calcium has been found and can be assessed in absolute numbers or after normalization for gender and age.[26-29] This is done because the degree of calcification in the coronary arteries may vary according to gender, age, and ethnicity, and certain values may be considered of greater or lesser relevance for each patient.[26-29] The usual way of interpreting the results of CA is shown in Table 1.[27-29.]

The importance of this approach for the risk stratification of asymptomatic patients was already reported in initial studies. Raggi et al. assessed 10037 patients, 903 of whom were diabetics, and found that CAC allowed the reclassification of the risk clinically estimated by conventional models.

Table 1. Classic model of interpreting the coronary calcium score.

Calcium score in absolute values	Calcium score in relative values after adjustment for gender, age, and ethnicity (percentile)	Degree of calcification
0	0	absent
1-10	1-25	minimal
11-100	26-50	discreet
101-400	51-75	moderate
401-1000	76-90	marked
>1000	>90	Highly marked

In the studied population, the score in diabetic patients was higher than that in individuals with normal blood glucose levels (281 ± 567 and 119 ± 341, $p < 0.0001$). However, the greater contribution of the test was observed in cases without coronary calcification. In this condition, the event-free survival rates of patients with or without diabetes at the end of 5 years of evolution was 98.8% and 99.4% ($p = 0.5$), respectively, showing the high negative predictive power of this index.[30]

Yeboah et al. analyzed the efficacy of CAC as a biomarker, comparing its efficacy against other forms of risk classifications. Reviewing the MESA study population, the authors found 1330 asymptomatic non-diabetic individuals with intermediate pretest likelihood who were subjected to several tests including C-reactive protein, measurement of the ankle-arm index, measurement of the mediated vascular response, IMT analysis, and CA.[31] With a median of 7.6 years of evolution, it was determined that family history, ultrasensitive PCR, ankle-arm index, and CAC predicted the incidence of events, with the latter element best discriminating between the cases at higher or lower risk.[32] Later, when analyzing 4955 patients also recruited in the MESA study, Gepner et al. confirmed that after 11.3 ± 3 years of evolution, the calcium score was higher than the other parameters used to identify cases at risk of having CE, but its efficacy was similar to that of ultrasound for identifying patients at higher probability of stroke.[33] The bioimaging study confirmed the efficacy of CAC but showed no superiority over ultrasonography in the identification of cases with worse prognosis.[17] In this study, the rate of reclassification using CA was higher for primary objectives (death from cardiovascular causes, stroke, and AMI - 0.25 vs. 0.23) and secondary objectives (death of any cause, stroke, AMI, unstable angina, and myocardial revascularization - 0.22 vs. 0.17), but this difference was not significant.[17]

A study of 23637 patients comparing the CAC with other risk factors proved the usefulness of this index because after a follow-up of 11.4 years, the evolution, especially regarding the incidence of AMI, was negatively affected by the presence of any degree of calcification.[34] However, a fundamental aspect that required consideration when implementing CAC as a biomarker was pointed out by Mitchell et al., who analyzed 13644 patients and observed that the use of statins reduced the number of events in patients with calcium in the coronary arteries but had no impact in cases of CAC = 0.[35] Moreover, the benefit brought by these drugs was proportional to the degree of calcification. In 10 years, 100 patients required treatment to reduce an event in cases of CAC between 1 and 100; only 12 with a CAC > 100 required treatment.[35]

Studies such as this recently influenced American associations to recommend in their guidelines that CAC be used to refine the risk stratification of patients with an intermediate pretest likelihood and that it guides the beginning of statin use, even in asymptomatic patients. When the CAC is 1–99, the authors state that it is reasonable to prescribe these drugs in patients aged 55 years or older and at any age if the CAC is greater than 100 or above the 75th percentile, both considering the level IIa recommendation.[36]

Despite its great clinical usefulness, CAC has limitations. It is important in asymptomatic cases, but there may be false-negative results in up to 20% of symptomatic patients that occasionally cause a significant reduction in the arterial lumen (Figures 3A and 3B).[37] Moreover, the total atherosclerotic load is better determined by angiotomography, which provides information about calcified and non-calcified plaques and has been considered an important marker of the clinical evolution of patients with the suspected or clinical diagnosis of obstructive coronary disease.[38] In a recent study evaluating the results of 1345 patients from an ongoing registry, Lee et al. reported that, considering the total number of plaques compromising the coronary arteries, enabled the finding of cases at higher risk, even in patients with plaques that reduced the vessel lumen by more than 50% and supporting the usefulness of this concept.[38] Despite these favorable results, studies unequivocally demonstrating the need to perform computed tomography angiography in asymptomatic patients are lacking, with this test being indicated in the presence of clinical elements or complementary tests confirming the clinical suspicion of obstructive coronary artery disease.

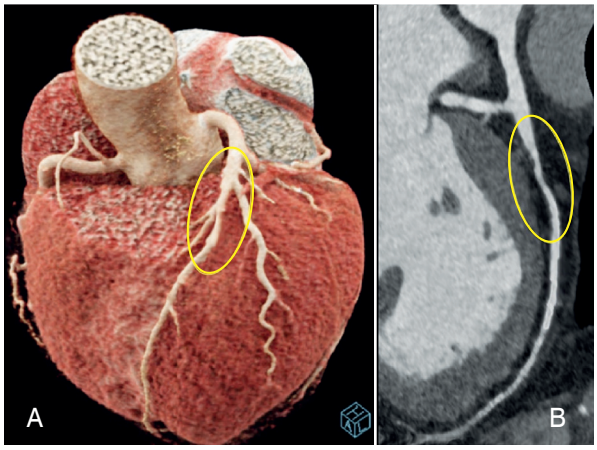

Figure 3. Some patients with symptoms or changes in response to non-invasive tests may have obstructions even without showing calcification points in the coronary arteries. This example shows a tomograph of a 54-year-old patient with palpitations and dizziness on exertion with ineffective exercise testing. Three-dimensional reconstructions (A) and longitudinal reformatting (B) show significant non-calcified plaques in the middle portion of the anterior descending artery. There were no calcification points in other segments of the coronary artery tree.

FINAL CONSIDERATIONS

The use of imaging methods improves risk stratification and enables the diagnosis of atherosclerosis even in the pre-clinical phase, which can positively impact event-free life expectancy. These methods make it possible to better identify cases that require rigorous lifestyle changes and statin use. The choice of method depends on the main objective of the investigation, equipment, and medical staff expertise. There are clear advantages of CA plaque investigation and quantification over IMT evaluation, and the investigation of coronary calcification degree is already recommended in recent international guidelines.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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