Review Article

Coronary CT Angiography in Asymptomatic Patients: Is There Evidence For Using It?

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Abstract

Cardiovascular diseases are the leading cause of death worldwide, and their clinical management is complicated by 3 main pathophysiological factors: a) a long onset period, often decades before a clinical event; b) a silent clinical course; and c) a multifactorial and heterogeneous pathogenesis among different population subgroups. Coronary CT angiography is the best available tool for diagnosing and phenotyping coronary artery disease, whether obstructive or non-obstructive. This allows early diagnosis and monitoring of the disease, which is essential for deciding who should be treated, determining the therapeutic approach, and for better patient adherence to clinical treatment. Early and accurate diagnosis generally results in better clinical outcomes.

"A straight path never leads anywhere other than the goal."

Andre Gide

Clinical case

A 48-year-old woman arrived for a routine check-up with no clinical complaints, but reported being worried because her mother (who was a smoker) had had a myocardial infarction at the age of 63. She had controlled hypertension (using 1 medication), was overweight (body mass index = 27), and was sedentary (but could climb 4 flights of stairs without stopping). The results of the physical examination were normal, as were those of a resting electrocardiogram. Her blood pressure was 118/64 mmHg. Her laboratory tests were all within normal limits. Her total cholesterol was 192 mg/dl; LDL-c: 125 mg/dl; HDL-c: 51 mg/dl; triglycerides: 80 mg/dl. The patient's Framingham score indicated a 2% risk of events in 10 years.

After discussion with the patient, the doctor requested coronary CT angiography (CCTA), which revealed non-calcified plaque with positive remodeling, resulting in 30-40% stenosis of the proximal anterior descending artery. There were no coronary calcifications (calcium score = 0).

In this case, should clinical treatment be initiated considering that the patient's clinical scores indicated low risk? Would CCTA findings help the patient make necessary lifestyle changes? Moreover, should a statin be introduced? If so, for which LDL-c target?

Keywords

Coronary Artery Disease; Computed Tomography Angiography; Asymptomatic Diseases.

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Manuscript received November 7, 2023; revised November 7, 2023; accepted November 7, 2023
Editor responsible for the review: Daniela do Carmo Rassi Frota

DOI: https://doi.org/10.36660/abcimg.20230091i

Introduction

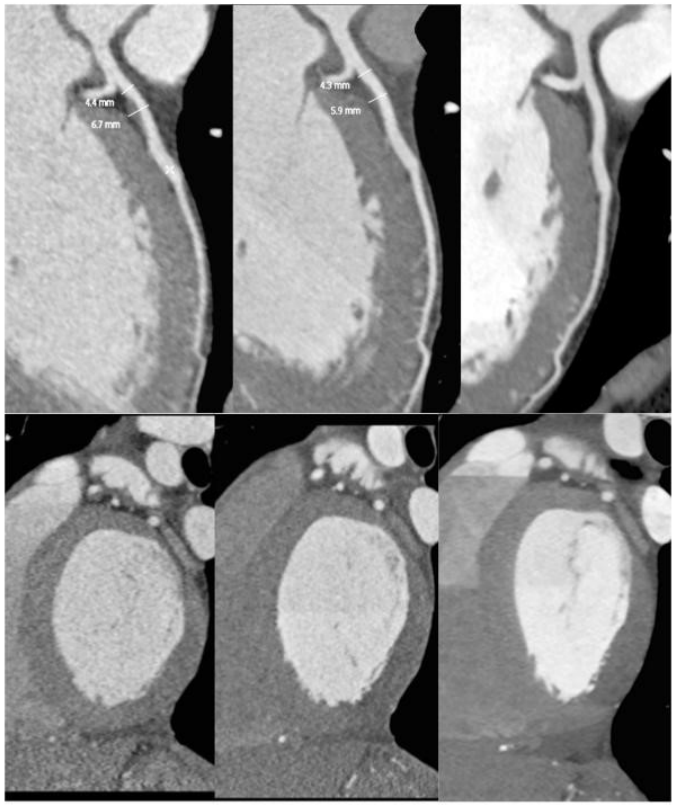
Cardiovascular disease is the leading cause of death worldwide. Although this fact is often repeated, far fewer people are aware that it kills more than the second, third, fourth, fifth, sixth, and seventh leading causes of death combined,[1] having great social and economic impact. Cardiovascular disease involves 3 pathophysiological factors that require more complex management: a) a long onset period, often decades before a clinical event; b) a silent clinical course; and c) a multifactorial and heterogeneous pathogenesis among different population subgroups.

Long onset period, often decades before a clinical event

Coronary artery disease (CAD) has a very early onset, often before the fourth decade of life. Pathology analyses in young adults < 35 years of age who died from trauma have found a > 70% prevalence of subclinical CAD, with a large proportion being obstructive CAD.[2,3] CAD is even present in 1 in 6 adolescents.[4]

Because its onset is so early and it has such a long clinical course, the most effective interventions are changes in patient lifestyle. Specific interventions, which are often expensive or have side effects, are not as effective. For example, consider carriers of PCSK9 gain-of-function mutations. Because it is a gain-of-function mutation in an enzyme that helps eliminate cholesterol, the cholesterol levels of these patients are on average 30% lower than matched controls, a reduction similar to that found in large studies on statins. However, unlike statins, these people are born with the mutation, ie, they spend their entire lives with lower levels of plasma cholesterol, while statins only reduce it after beginning therapy, and this reduction is subject to dosage irregularities inherent to all drugs. As a result, while statins reduce cardiovascular events by up to 30%, mutation carriers have a staggering 90% fewer events than matched controls.[5] This illustrates long-term power to reduce risk factors, in contrast to specific interventions. Graphing an imaginary patient's life, in which time is the abscissa and exposure to modifiable risk factors is the ordinate, the objective would be to reduce the area under the curve as much as possible, as shown in Figure 1.

Central Illustration: Coronary CT Angiography in Asymptomatic Patients: Is There Evidence For Using It?



Arq Bras Cardiol: Imagem cardiovasc. 2023;36(4):e20230091

Serial coronary CT angiography images (from left to right: baseline, 30 months, and 60 months) showing progressive plaque regression in the proximal left anterior descending artery. The upper images are multiplanar reconstructions and the lower images show transverse sections (arrows). The reference luminal diameter remained constant, but the tunica intima diameter decreased between baseline and 30 months, indicating decreased positive remodeling. There was also a progressive reduction in the degree of stenosis and total plaque volume.

Silent clinical course

Non-obstructive CAD causes no symptoms and has no warning signs. Even obstructive lesions (ie, > 50%) are, for the most part, asymptomatic. In addition, the fact that half of myocardial infarction patients never have suggestive symptoms before the event shows that a lack of symptoms does not indicate an absence of disease. On the contrary, when symptoms appear, they are a late sign, indicating an advanced stage of the disease. Between 50%–70% of young adults who have myocardial infarctions did not meet recommendations for statin use before the event.[6] In addition to a lack of symptoms, remaining undiagnosed also prevents therapy before an infarction.

Multifactorial and heterogeneous pathogenesis occurs among different population subgroups

Diseases such as mesothelioma, in which there is a strong association between exposure to agent (ie, asbestos) and the disease, allow for simple and emphatic recommendations. But this is definitely not the case with cardiovascular diseases, which have an extremely varied pathophysiology, a variety of risk factors with weak causal association, as well as heterogeneous heredity.

A study revealed that more than 400 genetic polymorphisms are associated with CAD,[7] possibly due to different degrees of penetrance for each variation, as well as epigenetic variations. More than 200 risk factors for CAD have been reported in the literature, although for the vast majority, despite being associated, the causal relationship is weak, ie, their relative importance in the development of CAD is low, except in rare conditions, such as some variants of familial hypercholesterolemia or specific genes of great penetration and pathogenicity. Additionally, different population groups are exposed to different environmental factors, and genotype/phenotype interactions vary. This is one reason why clinical scores have limited performance and high measurement variability, both for diagnosing obstructive CAD and predicting events.[8,9]

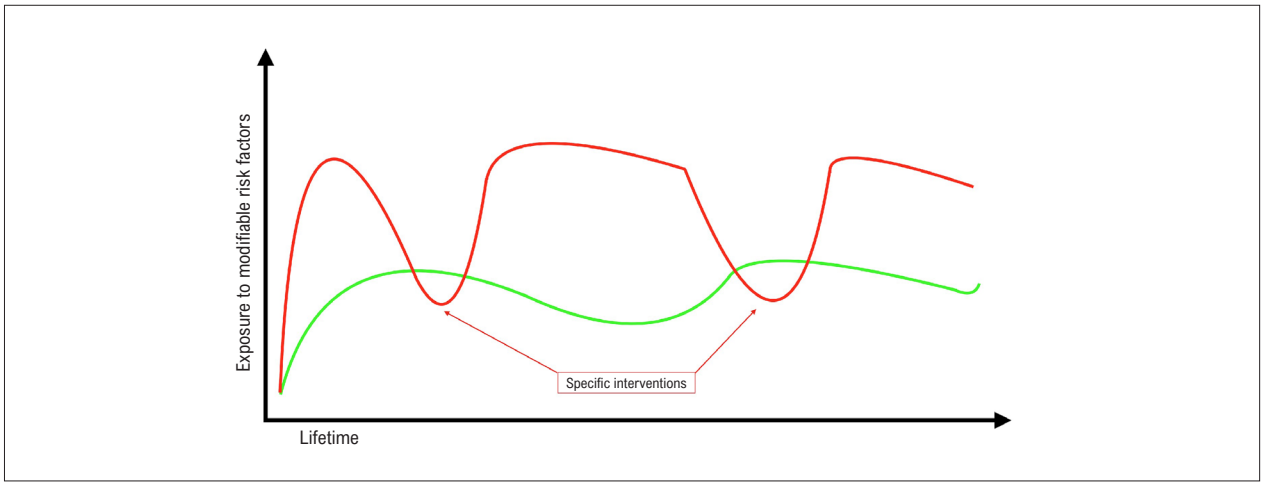


Figure 1 – *Model illustrating exposure to modifiable risk factors throughout life in 2 imaginary cases. The green line represents an individual who successfully minimizes exposure to risk factors, while the red line represents an individual with greater exposure who, at certain points, undergoes specific interventions. The objective is to obtain the smallest possible area under the curve, which is generally achieved in long-term rather than short-term interventions*

Furthermore, scores place great weight on age, since most events occur in older adults. However, as a result we lose the opportunity to diagnose atherosclerosis, change habits, and begin therapy in young people. If the goal is to reduce the area under the curve for risk factors throughout life, early diagnosis is essential.

Calcium score

The calcium score is a useful way of stratifying the risk of cardiovascular events and determining the therapeutic approach. The examination is simple to perform (although it requires specific tomography with ECG synchronization) and involves simple image reading and interpretation. Moreover, it does not require intravenous contrast or beta-blockers. The calcium score can independently predict cardiovascular events better than clinical risk factors or carotid intima-media thickness.[10] However, since it only detects the calcified part of the atherosclerotic plaque, positive results (above a discretionary cut-off point, most often 100 Agatston units) can only indicate preventive therapies. However, low calcium scores do not exclude coronary atherosclerosis, since non-calcified plaque is prevalent, especially in younger patients, who could derive the greatest long-term benefit from preventive measures. Perhaps because it does not exclude CAD, the Multi-Ethnic Study of Atherosclerosis cohort found that one-third of cardiovascular events occurred in patients with a calcium score of 0.[11] In the Coronary Artery Calcium Consortium cohort, 43% of cardiovascular deaths occurred in people without coronary calcium.[12] Aside from calcification being linked to age and the fact that its absence does not exclude CAD, the calcium score is not useful in longitudinal CAD assessment, since statin use may increase scores by increasing the calcified portion and decreasing the non-calcified portion of plaque.[13] The approximate 15% variability in measurements across 2 scans makes analysis of the clinical course problematic.[14,15]

CCTA

CCTA allows non-invasive detection of coronary atherosclerosis, accurately quantifying the degree of stenosis and identifying morphological markers of higher risk, such as positive remodeling, lipid content, punctate calcifications, and the "napkin ring" sign.[16] Currently CCTA is the first test performed when investigating symptoms suggestive of obstructive CAD. Since its sensitivity is > 95%, it is increasingly seen as a gatekeeper for invasive catheterization, which is especially relevant, considering that two-thirds of catheterizations do not involve obstructive CAD.[17] Symptoms suggestive of obstructive CAD do not interfere with the prognostic power of CCTA, with symptomatic and asymptomatic patients having the same event rate according to test results.[18]

CCTA is superior to the calcium score for determining prognosis in asymptomatic patients,[19] even in a subgroup of older adults[20] and people with diabetes.[21] In approximately one-third of asymptomatic patients without coronary calcification, CAD is confirmed by CCTA.[22]

Although investigating obstructive CAD is the main use of CCTA, being recommended by national and international guidelines, this may not be its most important role. CCTA is revolutionizing cardiology due to its ability to detect non-obstructive CAD, or in earlier stages of the disease, when long-term therapeutic results are more favorable, it can motivate patients to make difficult lifestyle changes.

CCTA in non-obstructive CAD.

CCTA is highly sensitive for detecting non-obstructive CAD, having good correlation with invasive measurements such as intravascular ultrasound and optical coherence tomography.[23] Plaque composition can be inferred non-invasively, identifying markers of cardiovascular event risk, such as positive remodeling (plaque growth towards the tunica externa is related to greater plaque inflammation), foci of hypodensity (fat has a low density in CT, therefore,

foci with a density < 30 HU are correlated with a higher lipid load).[24] Furthermore, the atherosclerotic burden can be assessed subjectively by visual analysis and reported using indices, such as the segment involvement score or the segment stenosis score, which are associated with cardiovascular events independently of calcium score or risk factors. More recently, semi-automated tools have been developed for coronary segmentation and atherosclerosis quantification, determining the percentage of calcified and non-calcified plaque, and identifying plaque with low density and positive remodeling.[25] Such tools are promising, although still little used in clinical practice due to the laboriousness of editing coronary contours.

Disease monitoring

Returning to the initially-described patient case, the physician decided to prescribe a statin (targeting LDL-c < 70 mg/dl) and outlined an intensive weight loss and exercise program, to which the patient adhered. The central figure details this patient's case, including 3 serial CCTAs (T = 0 [baseline]; T = 30 months, and T = 60 months) that showed progressive reduction of the arterial lesion. By the third examination (at 60 months), the lesion was virtually undetectable. Early detection of the disease allowed aggressive clinical intervention, which resulted in atherosclerosis regression.

Likewise, if subsequent CCTAs had shown disease progression, a frank conversation would have been necessary with the patient to show the therapeutic failure of current measures and the need for new course of action.

Since the disease is insidious and its clinical course is long, asymptomatic, and has a heterogeneous pathophysiology, the ability to monitoring atherosclerosis would be a powerful weapon for both doctors and patients.

Longitudinal studies involving CCTA have shown that cholesterol and glucose control result in low or no progression of the total coronary atherosclerotic burden, in addition to beneficial changes in plaque morphology, with a larger calcified component and an unchanged or reduced non-calcified component.[26,27]

When CCTA is normal

Normal CCTA results show an absence of plaque (calcified or non-calcified). This is valuable information, since the rate of cardiovascular events in people with normal CCTA results is extremely low (less than 0.1%/year), and remains low for ≥ 5 years (most likely for 10 years). Few therapies are cost-effective in this group of people. Obviously, healthy lifestyles should be encouraged, but statins should probably not be used, since to prevent a cardiovascular event the number needed to treat is prohibitively high.[28] Thus, an examination every 10 years might save the high long-term cost of continuous drug therapy.

Risks of CCTA

With current technology, the radiation dose from CCTA is similar to that of a chest CT (2–5 mSv). The biological risks arising from exposure to this type of radiation are uncertain, being based on theoretical calculations rather than empirical data. Further discussion is beyond the scope of this article, but, if there is a risk, it is very low.

The rate of severe allergic reactions to the intravenous iodinated contrast media used in CCTA is 1 in 17,000 injections. Contrast nephrotoxicity has been re-examined in light of new evidence: CT with intravenous contrast media was compared to CT without it. Rather than comparing renal function before and after applying contrast media, large new studies of more than 20,000 patients have compared those who underwent CT scans who did received contrast media with controls who did not. These studies found no post-examination differences in renal function between the groups, ie, nephrotoxicity could not be attributed to the contrast medium.[29,30]

Conclusion

Imaging screening for breast cancer, colon cancer, lung cancer, etc. is performed routinely and is recommended by large international societies. However, these diseases kill only a small fraction of those who die from coronary heart disease. The purpose of screening is early disease detection so that therapy can begin sooner, more assertively, and more effectively. Screening programs for any disease involve challenges related to selecting the population for screening, determining how to use the results, and documenting that the treatment strategy is associated with fewer events and improved prognosis, in addition to the program's costs and a number of other important issues. CAD, the leading cause of death worldwide, has an early onset, a long clinical course, and involves great pathophysiological heterogeneity. However, there are effective therapies for CAD. Thus, screening should be considered in light of these facts. CCTA is currently the best available tool for this purpose.

Author Contributions

Conception and design of the research; acquisition of data; analysis and interpretation of the data; statistical analysis; writing of the manuscript; critical revision of the manuscript for intellectual content: Gottlieb I.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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