Computed Tomography Coronary Angiogram; updates regarding evidence, clinical applications, and emerging technologies; a literature of review

Abstract:

Assessing of the coronary artery disease (CAD) especially coronary stenosis by coronary computed tomography angiography (CCTA) has shown a classic shift in the last decades. Recent advancements in cardiac CT have improved the quality of image and decreased exposure of patients to radiation. CCTA is a noninvasive technique for visualizing the anatomy of CAD. CCTA, in conjunction with newer applications such as plaque characterization and physiologic/functional evaluation, enables a comprehensive diagnostic and prognostic assessment of otherwise low-intermediate subjects for primary prevention. CCTA assesses overall plaque burden, distinguishes plaque subtypes, and identifies high-risk plaque with high reproducibility.

Evidence strongly recommends the use of CCTA all over the stages of CAD, early from detecting of minute subclinical diseases up to the estimation of acute chest pain. Furthermore, CCTA can be used to noninvasively quantify plaque burden and identify high-risk plaque, which can help with diagnosis, prognosis, and treatment. This is especially important in the evaluation of CAD in immune-driven conditions with a higher prevalence of cardiovascular disease.

Furthermore, key findings from large cohort trials have contributed to a better understanding of cardiovascular disease risk as a function of overall coronary plaque burden and the morphological appearance of individual plaques. With the introduction of CT-derived fractional flow reserve, an anatomical and functional test will be established within a single modality. Recent research has been published that looks at the short-term impact of CT-derived fractional flow reserve on downstream care and clinical outcomes. Furthermore, machine learning is a concept that is increasingly being applied to diagnostic medicine. Emerging CCTA applications based on hemodynamic indices and plaque characterization may provide personalized risk assessment, influence disease detection, and guide therapy further.

This review provides an update on the evidence, clinical applications, and emerging technologies related to CCTA. We also discuss how CCTA could be used to characterize coronary atherosclerosis, stratify asymptomatic subjects' prognosis, and guide medical therapy.

Keywords: coronary computed tomography, coronary atherosclerotic plaque, Computed tomography, Acute chest pain, Acute coronary syndrome, Myocardial infarction, Diagnostic triage, Review

Introduction:

CCTA is a useful noninvasive imaging modality that is becoming more widely regarded as the most important and the first test for diagnosing (CAD) and has prognostic consequences for patient management. CCTA can also be used to imaging anatomic different stages of atherosclerosis, early from formation of the plaque along through its progression and rupture especially in epicardial coronary arteries (1, 2). Also, it allows the least exposure to radiation(3, 4). CCTA has shown to have a highest diagnostic accuracy when compared with invasive coronary angiography (ICA), which has been the gold standard for evaluating coronary artery disease until now(5, 6).

CCTA-derived tools aid in risk stratification and medical decision-making for patients with CAD by allowing researchers to better comprehend the progression of atherosclerotic plaque. Minimal radiation exposure, effective coronary characterization, and thorough imaging of atherosclerosis over time have all been made possible thanks to advancements in CCTA. As a result, CCTA provides a central platform for a multidisciplinary approach that includes immunology, pathology, radiology, and cardiology to improve patient care and further our understanding of CAD.

Although many factors such as (e.g., arrhythmia, increase heart rate, and a high coronary calcium burden) may restrict overall evaluability, significant technological advancements in recent decades have opened new perspectives in cardiac imaging, allowing acquisition in a matter of seconds and with higher spatial resolution(7-10). On a per patient basis, a sensitivity and specificity of 98 percent and 90 percent, respectively, have been reported using at least a 64-slice multidetector row. To rule out obstructive coronary artery disease, the increased sensitivity translates into a negative predictive value (NPV) ranging from 95 to 100 percent (CAD)(11).

In this context, the severity of coronary stenosis is regarded as a powerful, albeit contentious, prognostic marker of CAD prognosis. Invasive and noninvasive angiographic studies have shown a link between stenosis severity and clinical outcomes Min et al. analyzed a large consecutive cohort of patients without a history of CAD and found a similar incidence of all-cause death in nonobstructive and 1-vessel obstructive CAD as measured by CCTA in a recent study (HR: 1.62 vs. 1.75)(12). Furthermore, non-obstructing lesions are thought to be responsible for more than two-thirds of acute myocardial infarction (MI)(13). Other factors, in addition to the degree of stenosis, have an important role in the course of events. Several clinical biomarkers and imaging modalities have been studied over the last few decades in the hopes of being able to predict events in individuals with plaques at high risk of rupturing (vulnerable plaque). While ICA focuses solely on determining the degree of coronary stenosis (lumino-graphy), CCTA consistently evaluates overall plaque burden, classifies plaque subtypes, and identifies unfavorable characteristics of coronary high-risk plaques by examining both the wall and the lumen of the coronary artery(11, 14).

Furthermore, CCTA may help us avoid a PCI in the case of obstructive CAD in a small vessel and begin early and vigorous medical therapy in the case of nonobstructive widespread CAD. The potential significance of CCTA as a noninvasive tool for mapping CAD, identifying nonobstructive lesions with signs of vulnerability, defining prognosis of otherwise low-to-moderate risk patients, and guiding therapeutic approaches is currently

generating more interest and controversy. Research in this field may pave the way for a new era of personalised risk prediction and medical treatment(10, 11). Indeed, because a variety of drugs, mostly those that affect the lipid profile and inflammation, can slow or even reverse plaque progression, the hunt for simple procedures that can detect these changes could provide physicians with a useful tool for patient management(4). World experts in CCTA gathered in November 2019 at the National Heart, Lung, and Blood Institute for a summit to discuss the newest discoveries in the area, consolidate the current research, and debate the evolving clinical applications of CCTA. The European Society of Cardiology advocated CCTA as an alternative to stress imaging modalities for patients with suspected stable CAD and a low-to-intermediate pretest risk of CAD in 2013. The NICE-UK guidelines on the care of patients with new onset chest pain were recently updated, and CCTA was advocated as a first-line diagnostic test for persons whose stable angina could not be ruled out by clinical examination alone.

Moving beyond coronary stenosis, the current review will discuss the characteristics of coronary susceptible plaques as well as the capacity of CCTA to perform noninvasive plaque characterization with practical prognostic implications in patient risk assessment. In addition, existing and future therapeutic views are discussed.

Literature of review:

1- Vulnerable plaque and its Characteristics by CCTA:

Histologic studies indicate that plaque composition is important in the pathogenesis and clinical outcomes of epicardial lesions. The morphology, composition, and degree of inflammation of coronary atherosclerotic plaques, according to expert consensus, are more important than the degree of luminal stenosis(11).

It is critical to recognize the precursor lesions of acute coronary syndromes (ACS) if advances in ACS are to occur(15, 16). The majority of ACS are thought to be the result of a sudden luminal "thrombosis" caused by one of three different pathologies. Plaque rupture is the most common cause of thrombosis, followed by plaque erosion. Dense calcified nodules, which are less common, can penetrate the fibrous cap and cause thrombosis. Plaque rupture is the most common cause of coronary thrombosis in both genders, accounting for approximately 76 percent of all fatal coronary thrombi(17). As a result, while the term "vulnerable plaque" should be reserved globally for plaques that resemble all three causes of luminal thrombosis, it is usually restricted to a rupture-prone plaque(18, 19).

Early in the disease process, intimal thickening is observed. The early lesion is made up of smooth muscle cells and is influenced by an increase in macrophage and lipid influx. The formation of a necrotic core and the development of a fibrous cap atheroma represent the next phase. A certain amount of lipid and apoptotic macrophages can be found in the necrotic core. Intraplaque hemorrhages are also common in this entity and contribute to further lipid core enlargement. A fibrous cap that is stable may prevent the lesion from rupturing. A thin cap atheroma can develop if the fibrous cap loses matrix proteins and smooth muscle cells(20, 21). Cardiac computed tomography angiography (CTCA) has emerged as a promising tool for direct visualization of the vascular lumen. The CCTA focuses on validated measures of plaque vulnerability. Its potential role as a "noninvasive" method for mapping coronary atherosclerosis is gaining attention(22).

2. prognosis after localizing and detecting degree of stenosis

Despite advances in preventive approaches and therapies, coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality in both industrialized and low- to middle-income countries. Sudden cardiac death has been reported in 50% of men and 64% of women who had no previous cardiovascular symptoms(11). The severity of coronary stenosis is a powerful but still debatable predictor of prognosis. A large number of studies have confirmed CCTA's long-term prognostic power in predicting excellent prognosis in patients (including diabetics) without coronary plaques and intermediate prognosis in patients with nonobstructive lesions. Event-free survival rates of symptomatic patients with CT-diagnosed CAD decreased proportionally from normal coronary arteries (98.3 percent) to nonobstructive (95.2 percent) to obstructive CAD (87.5 percent) in a long-term follow-up(21).

Similarly, Cheruvu et al. reported that in the CONFIRM registry's very low risk cohort of patients followed for a mean of 5 years, the incidence of major adverse cardiovascular events (MACE; all-cause death, nonfatal MI, unstable angina, or late coronary revascularization) increased from 5.6 percent in those without CAD to 13.24 percent in those with nonobstructive disease and 36.28 percent in those with obstructive disease (p0.001)(23).

The novel coronary artery disease-Reporting and Data System (CAD-RADS) scores used to standardize CCTA reporting classified CAD stenosis severity as 0 (0 percent), 1 (1 percent to 24 percent), 2 (25 percent to 49 percent), 3 (50 percent to 69 percent), 4A (70 percent to 99 percent in 1 to 2 vessels), 4B (70 percent to 99 percent in 3 vessels or 50 percent left main), or 5 (50 percent left main) (100 percent). It should come as no surprise that CAD-RADS effectively identifies patients at risk for adverse events. For CAD-RADS 0 to 5, cumulative 5-year event-free survival ranges from 95.2% to 69.3% (p 0.0001). Higher scores are related to increased event risk (hazard ratio: 2.46 to 6.09; p 0.0001). Its inclusion in coronary CTA reports could present a novel opportunity to promote evidence-based care(24).

Ahmadi et al. demonstrated that the survival rate of subjects with nonobstructive CAD decreases significantly with the number of diseased coronary arteries (from single to triple vessel disease, p0.001) and is affected by plaque morphology. The death rate rises incrementally from calcified plaque (1.4%) to mixed plaque (3.3%) to no calcified plaque (0%). (9.6 percent). When compared to calcified plaques, the risk-adjusted hazard ratios for all-cause mortality were 3.2 (95 percent confidence interval 1.3 to 8.0, p=0.001) for mixed plaques and 7.4 (95 percent confidence interval 2.7 to 20.1, p=0.0001) for noncalcified plaques. The death rate in subjects with mixed or calcified plaques increased with the severity of coronary artery calcium, from 1 to 9 to > 400(25).

High-risk plaque (HRP) characteristics have also been linked to an increased risk of events in patients with nonobstructive CAD. A recent study found that using an integrated score easily obtained with CCTA (based on the presence of mixed and remodeled atherosclerotic plaques) may improve MACE prediction in symptomatic patients without prior cardiovascular history but with intermediate pretest likelihood of CAD, beyond standard clinical (Diamond & Forrester) and coronary (based on presence and degree of stenosis) scores used in clinical practice. Even with the low prevalence of some high-risk plaque characteristics, this finding emphasizes the importance of a comprehensive coronary evaluation(26).

There is no way of knowing which plaques with high-risk characteristics will rupture and cause events. However, the prognostic value of risk assessment based solely on plaque anatomy has been partially disappointing due to a low positive predictive value(27).

3. future improvement and prognosis

Noninvasive functional testing should be used as a gatekeeper to catheterization in patients with suspected or known disease. Fractional flow reserve may be considered instead for determining the hemodynamic significance of a coronary lesion with moderate stenosis (50 percent -90 percent)(13, 28)

Characterization of plaques may be useful for clinical purposes. When adjusted for stenosis severity, plaque remodeling remained a predictor of ischemia for all degrees of stenosis, according to Park et al. Similarly, it has been reported that the prevalence of PR, LAP, and SCs was three to fivefold higher in moderately stenotic vessels perfusing ischemic territories than in vessels without ischemia. The pathogenetic mechanism underlying HRP features and inducible ischemia in moderate anatomic stenosis remains unknown. It has been proposed that the necrotic core is to blame for oxidative stress. Local inflammation may impair the production and bioavailability of the vasodilator nitric oxide while increasing the levels of vasoconstrictors such as iso-prostanes(29, 30). CTA with newer applications may be the Holy Grail for a comprehensive coronary disease assessment. Stress myocardial computed tomography perfusion (CTP) and fractional flow reserve CT (FFRCT) have recently been introduced in the clinical field for evaluating the functional relevance of stenosis by cardiac CT. Gaur et al. showed that plaque tissue characterization and FFR-CT improve the ability to predict inducibility of ischemia in a myocardial territory dependent on a specific coronary lesion compared to mere luminal stenosis assessment.

4. Therapeutic Viewpoint

Patients who undergo CCTA have a significantly lower risk of mortality, revascularization, and incident MI. This could be due to an increase in the use of preventive therapies (such as aspirin and statins) among patients with stable chest pain and nonobstructive CAD(22, 31, 32).

If target low-density lipoprotein (LDL) cholesterol levels are met, statin therapy can slow the rate of plaque progression and induce a small amount of coronary atherosclerosis regression. The use of atorvastatin to lower LDL cholesterol levels to 80 mg/dl was associated with no increase in coronary plaque burden(33, 34).

Historically, cardiac CT has played a role in risk stratification via the Coronary Artery Calcification Score (CAC). CAC is strongly linked to an increased risk of cardiovascular disease. Once coronary calcification begins, it progresses in a predictable pattern, with no consistent evidence of the ability to regress in response to therapy. Although the standard CAC score appears to have no role in evaluating therapeutic response or change in atherosclerotic disease over time, new CAC scoring approaches that distinguish calcium density from volume may provide a significant assessment of therapeutic changes, supporting the widely held (but unvalidated) belief that calcification plays a role in plaque stabilization.(35)

Inoue et al. demonstrated that the use of statins, even at low doses, resulted in a reduction in plaque quantity and necrotic core volume in a preliminary study on 32 patients who underwent CCTA with suspected coronary artery disease. Interestingly, changes in plaque morphology can occur even with relatively minor changes in the lipid profile and early in the course of downstream statin treatment(35).

Statins can slow the progression of mild noncalcified coronary plaque and induce plaque regression. Statin therapy is more likely to benefit patients with a higher baseline plaque burden and basal hyperlipidemia. These findings could have far-reaching implications for disease prevention strategies(36). Although serial scans cannot currently be recommended to monitor the therapeutic efficacy of medical interventions, plaque modulation as part of risk modification is a viable strategy. Direct visualization of the natural course of atherosclerosis, as well as identification of clinical determinants of plaque progression or regression, has the potential to change the paradigm of CAD monitoring in low- to moderate-risk patients with suspected CAD, with the goal of offering earlier therapeutic strategies. It is reasonable to believe that a significant reduction in plaque vulnerability through therapeutic intervention should contribute to plaque stability and, as a result, lower cardiovascular event rates. More research is needed to fully understand this issue.

6-CCTA in Clinical Practice

In the United States, CCTA is used in a variety of settings, including the evaluation of suspected ACS in the emergency room, planning before cardiac surgery, monitoring ischemic functional tests, and preceding lower-probability catheterization cases. CCTA can also be used as part of the cardiac evaluation process prior to liver transplantation(37, 38).

CCTA may be a better predictor of obstructive CAD compared to traditional functional testing. Clinical utility is driven by its ability to effectively rule out CAD. A CCTA-first strategy significantly reduced the occurrence of myocardial infarction (MI) and coronary heart disease death without increasing invasive testing(39, 40).

CCTA is critical in the emergency setting, where approximately 7 million emergency department visits for chest pain occur each year, accounting for 5.4 percent of all visits and $10 billion in annual spending. Despite the fact that the majority of these presentations are noncardiac in nature, missed diagnosis of acute MI accounts for significant mortality and a significant proportion (20%) of emergency medicine litigation costs(41). Several multicenter clinical studies in the emergency setting have shown that CCTA is a safe, quick, and effective tool for ruling out CAD in patients at low to intermediate risk who present with acute chest pain, and it is associated with a shorter time to diagnosis and a shorter length of stay(42).

Conclusions:

CCTA could be able to monitor and guide the therapeutic approach which is the ultimate goal of events prediction. Early identification of CAD, characterization of atherosclerotic process, evaluation of ischemia-related plaque features, and assessment of "vulnerable plaque" are mandatory endpoints.

The ability of CCTA to quantify coronary plaque composition and identify coronary plaque morphology will aid in therapy monitoring and may one day become a cornerstone in treatment personalization. Emerging technologies that take advantage of lower radiation doses, advances in feature extraction, and computational fluid dynamics have increased CCTA's prognostic value.

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