Current understanding of coronary artery calcification

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Abstract

Coronary artery calcification (CAC) is highly prevalent in patients with coronary heart disease (CHD) and is associated with major adverse cardiovascular events. There are two recognized types of CAC—intimal and medial calcification, and each of them have specific risk factors. Several theories about the mechanism of vascular calcification have been put forward, and we currently believe that vascular calcification is an active, regulated process. CAC can usually be found in patients with severe CHD, and this asymptomatic phenomenon makes early diagnosis of CAC important. Coronary computed tomographic angiography is the main noninvasive tool to detect calcified lesions. Measurement of coronary artery calcification by scoring is a reasonable metric for cardiovascular risk assessment in asymptomatic adults at intermediate risk. To date, effective medical treatment of CAC has not been identified. Several strategies of percutaneous coronary intervention have been applied to CHD patients with CAC, but with unsatisfactory results. Prognosis of CAC is still a major problem of CHD patients. Thus, more details about the mechanisms of CAC need to be elucidated in order to improve the understanding and treatment of CAC.

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1 Introduction

Coronary artery calcification was previously thought to be a benign process, and the calcified lesion increases in accordance with aging. Subsequently, studies determined that medial calcification is associated with arterial stiffness, which increases risk for adverse cardiovascular events. Further studies showed that the extent of coronary artery calcification (CAC) strongly correlated with the degree of atherosclerosis and the rate of future cardiac events, and the high prevalence of CAC in coronary heart disease (CHD) patients makes percutaneous coronary intervention (PCI) difficult to perform. The present article reviews the current studies in CAC which focuses on the pathogenesis and strategies to manage CAC.

2 Epidemiology and risk factors

The prevalence of CAC is age- and gender-dependent, occurring in over 90% of men and 67% of women older than 70 years of age. Additionally, people who have higher body mass index, higher blood pressure, abnormal lipids (higher low density lipoprotein or triglycerides, lower high density lipoprotein, or use of lipid-lowering medication), glucose disorders (impaired fasting glucose, untreated or treated diabetes mellitus), a familial history of CAC, chronic kidney disease (CKD), higher fibrinogen level and higher C-reactive protein level are more susceptible to CAC. Two recognized types of CAC are intimal or superficial and medial artery calcification. Atherosclerotic calcification mainly occurs in the intima. Inflammatory mediators and elevated lipid content within atherosclerotic lesions induce osteogenic differentiation of vascular smooth muscle cells.
(VSMC). Conversely, CAC in the media is associated with advanced age, diabetes, and CKD. Several studies have confirmed that advanced age, diabetes mellitus, dyslipidemia, hypertension, male gender, cigarette smoking and renal disease are risk factors of intimal calcification. On the other hand, renal dysfunction (mostly reduction of glomerular filtration rate), hypercalcemia, hyperphosphatemia, parathyroid hormone abnormalities and duration of dialysis are connected to medial calcification. 

3 Pathogenesis

CAC results in reduced vascular compliance, abnormal vasomotor responses, and impaired myocardial perfusion. The pathogenesis of CAC and bone formation share common pathways, and risk factors have been identified which contributed to the initiation and progression of CAC. Although a majority of the studies demonstrated that calcium intake had no significant adverse or beneficial effect on vascular calcification and cardiovascular endpoints, dietary calcium intake above the median of 805 mg/d was associated with an increased risk of myocardial infarction (MI). However, one should not cease consumption of calcium supplements at recommended levels when adequate dietary calcium intake cannot be achieved. Fetuin-A is a hepatic secretory protein that inhibits arterial calcification in vitro. While the association of fetuin-A with CAC in the general population is uncertain, fetuin-A is inversely associated with CAC severity among community based individuals without cardiovascular disease (CVD).

Vascular calcification is an active and regulated process. Several theories on the mechanisms of vascular calcification have been put forward, including distributed Ca/Pi imbalance (hyperphosphatemia, hypercalcemia), induction of bone formation (vascular bone and cartilage-like cells), presence of apoptotic bodies, circulating nucleational complexes and loss of inhibitions (e.g., pyrophosphate, matrix glycoprotein, oxypropionitrile, Fetuin/alpha2-HS, glycoprotein). In fact, VSMC plays an integral role in this process by undergoing trans-differentiation to osteoblast-like cells, elaborating calcifying matrix vesicles and secreting factors that diminish the activity of osteoclast-like cells with mineral resorbing capacity. The receptor activator of nuclear factor-kappaB ligand/osteoprotegerin pathway has emerged as a potential link between osteoporosis and CAC. However, the entire mechanism of CAC progression has not been fully elucidated.

Recent advances have identified microRNAs (miRs) as key regulators of CAC by directing the complex genetic reprogramming of smooth muscle cells (VSM) and the functional responses of other related cell types relevant for vascular calcification. The transcription factor, osterix, was identified as a miR-125b target, and inhibition of miR-125 was associated with increased Runx2 and osterix expression, as well as increased alkaline phosphatase activity and SMC calcification. Other studies found that miRs that targeted Runx2, including miR-133 and miR-204, were down-regulated in murine aorta SMC, leading to calcification in vitro. Members of the bone morphogenetic protein (BMP) superfamily also are known regulators of calcification, and BMP2 and BMP4 are recognized as osteo-genic differentiation factors identified in calcified atherosclerotic vessels. It is also known that the wingless-type mouse mammary tumor virus (MMTV) integration site family member (Wnt) is required for osteoblast function and is involved in SMC trans-differentiation. Mechanistic studies also revealed the role for local vascular Klotho as an endogenous inhibitor of vascular calcification. Studies have identified miR-223 as an important regulator of vascular calcification in VSMC exposed to high level of inorganic phosphate. Murine aorta SMCs grown in calcification medium for nine days were studied using miR microarrays and identified more than 100 differentially-expressed miRs. Of these, several miRs (miR-221, 222, 24-2, 27a and 31) were confirmed to be down-regulated in vitro. Further investigation revealed that miR-221 and miR-222 acted synergistically to induce calcification. Further studies that identify master regulatory miRs are needed so as to target miRs as a potential option of therapeutic intervention.
CAC is not only independently associated with CHD of asymptomatic subjects, but also carries prognostic importance in patients with known CHD and has demonstrated in multiple intravascular ultrasound studies that the average number of calcium deposits within an arc of < 90 degrees per patient was significantly higher in patients with acute MI than with stable angina. Conversely, calcium deposits were significantly longer in patients with stable angina, in contrast to the typical pattern of spotty calcification in acute MI.

CACS was first reported by Agatston, et al.,[33] and is one of the most commonly used methods to evaluate coronary atherosclerotic burden. Agatston scores were divided into three groups: a CACS between 0–100, 101–400, and more than 400. And CACS > 400 has significant prognostic implications in specific patient groups. The study by de Araujo, et al.,[34] had shown that there was a significant difference in CAC-score between patients with atypical chest pain with and without diabetes mellitus [68 (0–311) vs. 0 (0–67), \( P < 0.001 \)]. In asymptomatic adults (40 years of age and older) with diabetes, measurement of CAC is reasonable for cardiovascular risk assessment.[35–38] Those with CAC > 100 were 2–5 times at higher risk of suffering an acute CHD event in the near-term follow-up.[39] In large-scale observational studies, CACS added prognostic value in predicting cardiac death and MI, especially in patients at intermediate risk for events.[40,41] Research also showed that CACS has a positive relationship with ECG and atherosclerosis and increased incidence of elevated lipoprotein.[39] Most importantly, CACS plays an important role in reclassifying individuals with intermediate risk of CHD. This is crucial as most cardiovascular events occur in individuals with intermediate risk, and intervention to reduce risk among individuals at high risk are better established than those with intermediate risk.

Measurement of CACS is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk of CHD (10%–20%, 10-year risk).[42] The area under the receiver-operating characteristic curves showed the incremental value of CACS and CTCA for predicting MACE, 0.71 for clinical risk factors, which improved to 0.82 by adding CACS and further improved to 0.93 by adding CTCA (both \( P < 0.001 \)).[43] Therefore, assessment of CACS and coronary CTA have prognostic value and have incremental value over routine risk factors for MACE, and CTCA is superior to CACS alone. There are more studies that confirmed the prognostic value of cardiac CTA.[43,44] But CTCA is not recommended for cardiovascular risk assessment in asymptomatic adults.[45]

### 5.2 Intravascular ultrasound

Intravascular ultrasound was determined to be the gold standard of CAC because of its high sensitivity (90%) and specificity (100%). According to the range of calcified lesion, CAC was classified into 4 classes through detection by intravascular ultrasound: Class I, 0°–90° calcification; Class II, 91°–180° calcification; Class III, 181°–270° calcification; and Class IV > 270° calcification.

### 5.3 Optical coherence tomography (OCT)

OCT also has high sensitivity and specificity to identify CAC. Moreover, optical coherence tomography can be used to assess thickness and volume of calcification since light penetrates calcium.

### 6 Prognosis and treatment

There is no established treatment for CAC to date. In the St. Francis Heart Study, 1,005 patients with CACS > 80th percentile for the age and gender were randomized to atorvastatin 20 mg daily or placebo.[46] Atorvastatin resulted in reduced low-density lipoprotein cholesterol levels and an insignificant decline in MACE, but had no effect on CAC progression. Calcium-channel blockers,[47] hormonal therapy,[48] phosphate binders,[49,50] and most recently, medicinal supplements[51,52] have all been suggested to reduce CAC progression in small randomized trials, though large multicenter trials are needed to confirm these findings. Although several studies had shown that traditional Chinese medicine treatment has therapeutic value on coronary atherosclerotic heart disease, no study has been done to address whether traditional Chinese medicine has an effect on CAC.

CAC makes PCI difficult to operate. There have been identified 16 randomized, controlled trials with 23,481 patients and a mean follow up of 18 months which examined...
the impact of CAC on prognosis after PCI. Data revealed that severe coronary calcification resulted in less complete revascularization (48% vs. 55.6%, \(P < 0.001\)), and was associated with higher mortality (10.8% vs. 4.4%, \(P < 0.001\)), higher rate of death and MI (23.2% vs. 10.9%, \(P < 0.001\)), and higher rate of coronary revascularization (31.8% vs. 22.4%, \(P < 0.001\)). Therefore, CAC appears to be an independent predictor of worse prognosis.\(^{54}\)

Several strategies of PCI including balloon angioplasty, cutting balloon, rotational atherectomy, stenting, post-dilation and Laser have been used in patients with CAC.

### 6.1 Balloon angioplasty

CAC increases the likelihood of procedural failure and complications after balloon angioplasty.\(^{52}\) Besides, the force applied from the balloon to the vessel wall might not be uniform across the length of the lesion, due to varying amounts of calcification, which increases the risk for dissection and acute vessel closure, MI, restenosis, and MACE.\(^{55}\) It is recommended that when the pressure of the balloon has achieved 16 atm and if the calcified lesion still could not be optimally expanded, stenting should not be performed. In the report of Diaz, et al., eight patients with calcified, non-dilatable lesions were treated with a double-layered, noncompliant, extremely high-pressure balloon. This balloon could be used at 40 atm and achieved 75% success rate without any adverse sequelae, thus providing a new way of dilating lesions or under-expanded stents when other non-compliant balloons have failed. When performing balloon angiography for severely calcified lesions, several strategies are suggested: small size balloon is preferred; pressure of balloon angiography from 8 atm is preferable, and the pressure should be slowly increased; the upper limit of pressure should be 16 atm for regular balloon, though higher pressure can be employed for noncompliant balloon (40 atm for OPN NC balloon, Case report\(^{56}\); and an awareness of complications of flow restricting dissection or perforation.

### 6.2 Cutting and scoring balloons

Cutting and scoring balloons do not remove calcium in the coronary artery. However, they improve vessel compliance by creating discrete incisions in the atherosclerotic plaque, enabling greater lesion expansion and reducing recoil while preventing uncontrolled dissections.\(^{57}\) The cutting and scoring balloon scan should be performed on lesions with mild to moderate CAC. The indication for cutting balloon is that the lesion is relatively short (< 20 mm). However, for class III-IV lesions according to intravascular ultrasound, a cutting and scoring balloon procedure is not recommended. Furthermore, the pressure of the cutting balloon should not exceed 12 atm in order to avoid embedding the cutting razor into the vessel wall.\(^{58-60}\)

### 6.3 Drug eluting stent (DES) vs. bare metal stent (BMS)

Randomized clinical trials showed that paclitaxel-eluting stents significantly reduce restenosis in patients with coronary calcified lesions compared with BMS. The TAXUS-IV (slow-release, polymer-based, paclitaxel-eluting stent) trial was a prospective, double-blind, randomized, multicenter study which examined the impact of calcified lesion on clinical and angiographic outcomes after paclitaxel-eluting stent implantation. The rate of ischemia-driven, target lesion revascularization at one year was reduced by 56% in patients with calcified lesions (11.9% vs. 5.1%, \(P = 0.09\)) and by 75% in non-calcified lesions (15.7% vs. 4.3%, \(P < 0.0001\)).\(^{61}\) On the other hand, a study had recruited approximately 2,000 patients, they were followed over the past 10 years to examine trends in PCI, it was concluded that the implantation of DES in patients with moderate to severe calcified lesions was safe and was associated with a significant reduction in the risk of repeat revascularization when compared to those receiving BMS.\(^{62}\) A meta-analysis of five trials with 2,440 patients (1,230 in the DES group, 1,210 in the BMS group) showed that DES significantly reduced target lesion revascularization rates compared to BMS in patients with calcified coronary lesions (8.5% vs. 16.0%; odds ratio: 0.50; 95% CI: 0.38–0.65; \(P < 0.0001\)). There was no significant difference in terms of the incidence of stent thrombosis, cardiac death and MI.\(^{63}\)

### 6.4 Rotational atherectomy

Unlike cutting balloon, the rotational atherectomy device abrades hard tissue into smaller particles (< 10 \(\mu\)m) while deflecting off softer elastic tissue.\(^{64}\) Therefore, rotational atherectomy has a selective effect on hard lesions, but not the soft tissues. In the pre-stent era, the use of rotational atherectomy alone was associated with increased neo-intimal hyperplasia, restenosis, and repeat revascularization, which was most likely due to platelet activation and thermal injury.\(^{65}\) Moreover, patients with calcified lesions undergoing rotational atherectomy are at increased risk for thrombus formation and slow or no reflow, with increased rates of periprocedural MI.\(^{66}\) The optimal burr size is 60%–70% of the reference vessel diameter. Smaller burr sizing reduces angiographic complications and periprocedural release of creatine kinase-myocardial band with similar procedural and angiographic success, when compared with more aggressive burr sizing (burr-to-artery ratio > 0.7). Furthermore, smaller burrs permit the use of smaller guiding catheters and radial approaches which lead to fewer vascular complications. So-
suitable for balloon angioplasty in the DES era. It was observed that the middle term survival was worse among patients undergoing rotational atherectomy than those without. On the other hand, rotational atherectomy was undertaken in patients with higher pre-procedural risk (older, higher incidence of diabetes, hypertension and peripheral arterial disease). Generally rotational atherectomy remains clinically useful for patients with calcified coronary lesions.

The DES is recommended after rotational atherectomy in order to achieve a better prognosis. Recent case series have reported intermediate and long-term outcomes after DES with adjunctive rotational atherectomy. Most of these studies reported a target lesion revascularization rate of ≤10% within one to two years. There was no difference in the long-term clinical outcomes between sirolimus and paclitaxel-eluting stents following rotational atherectomy. For severely calcified lesions that necessitate rotational atherectomy, thin-strut DES resulted in lower rates of target vessel revascularization when compared to thick-strut DES.

6.5 Laser coronary atherectomy

Excimer laser coronary atherectomy (ELCA) can dilate resistant lesions through a photoacoustic mechanism. Although this technique has been introduced for more than two decades, due to the uncertain outcomes and with the advent of DES, it has lost favor and use is limited to a few centers with selected patient and lesion cohorts. Potential procedural complications, such as vessel dissection (especially with superficial calcium) and perforation, as well as higher rates of restenosis were exhibited in some studies. Recently, several modifications in ELCA technology have been made to further improve procedure outcomes and safety. ELCA could be an alternative solution with acceptable performance in the treatment of complex coronary lesions, such as moderate calcification, not suitable for balloon angioplasty in the DES era.

6.6 Orbital atherectomy

Similar to rotational atherectomy, orbital atherectomy exploits a differential ablative effect on hard and soft surfaces, producing particles of <2 μm in size while exerting a centrifugal force on the vessel wall. The device allows interventionists to control ablation depth by increasing rotational speed (ranging from 60,000 to 120,000 rpm) which translate to a larger orbit of rotation. Like rotational atherectomy, orbital atherectomy improves the compliance of calcified lesions to reduce procedural complications and facilitate stent implantation. Studies had shown that preparation of severely calcified plaque with the Orbital Atherectomy System not only helped facilitate stent delivery, but also improved both acute and 30-day clinical outcomes compared with the outcomes of historic control subjects in this difficult-to-treat patient population.

6.7 Coronary artery bypass graft surgery

Coronary artery bypass graft surgery is recommended in patients with class III to IV CAC based on intravascular ultrasound, as well as anticipated difficulty in performing PCI which include the following characteristics: (1) thrombotic or ulcer lesions, (2) serious angle lesions > 60 degrees, especially into more than 90 degree angle, (3) have obvious intimal tear lesions, (4) diffuse lesion length > 25 mm, (5) severe left ventricular dysfunction, and (6) the coronary guidewire cannot transit the calcified lesion. Of note, patients with CAC are more likely to develop calcified saphenous vein grafts, a strong predictor of early and late graft failure. Therefore, the result of coronary revascularization is less favorable in patients with significant CAC.

7 Conclusions

Despite a significant amount of research addressing CAC, our understanding of the pathogenesis, clinical implication and management of CAC remains limited. In terms of pathophysiology of CAC, the governing factors are not fully understood regarding formation of intimal versus medial calcification, and the clinical significance of these two types of CAC remains to be elucidated. On the other hand, CAC carries prognostic importance. Coronary CTA is an established tool to assess CAC, and a score >400 is associated with worse clinical outcomes in patients with an intermediate risk of developing CHD and in those with established CHD. Currently, there is no specific medical therapy targeting the reduction of CAC, and whether the treatment strategy limits the progression or enhances the regression of CAC or has prognostic impact needs further clinical studies. On the other hand, in patients with CHD and significant coronary stenosis which necessitate revascularization therapy, the presence of moderate to severe CAC pose a clinical challenge. Specifically, developed PCI strategies have contributed to significantly higher procedure success, though morbidities are usually higher than in those patients without CAC as a result of the increased complexity of the procedures and higher cardiovascular risk profiles. Future studies should focus on the understanding of pathophysiological mechanisms of CAC, identify targets of potential therapy, and improve interventional strategies.
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