Coronary Calcification: Types, Morphology and Distribution

Michelle C Morris and Rolf P Kreutz

Division of Cardiovascular Medicine and Krannert Cardiovascular Research Center, Indiana University School of Medicine, Indianapolis, IN, US

Abstract

The development and progression of coronary calcification is of growing interest with the emergence of new imaging modalities and calcium modifying technologies that can facilitate optimal results during complex percutaneous coronary intervention (PCI). Coronary atherosclerotic disease typically begins within the intima with pathological intimal thickening and microcalcifications (>0.5 µm and <15 µm). These microcalcifications can coalesce into larger areas of calcification, including sheet calcium, which is typically seen in fibrocalcific plaque, nodular calcification and calcified nodules. Calcified nodules typically protrude into the vessel lumen. Erosive calcified nodules lack the coverage of protective anti-aggregatory endothelium and frequently show adherence of intraluminal thrombus. Greater calcification within coronary plaque does not correlate with an increased risk of acute coronary syndrome, however, coronary calcium can lead to challenges with stent delivery and full stent expansion during PCI. An understanding of plaque morphology, distribution of calcium, degree of calcification and underlying shape will enable interventional cardiologists to appropriately interpret intravascular ultrasound and optical coherence tomography imaging findings and optimise results during complex PCI.

Keywords

Intimal calcification, fibroatheroma, calcified nodule, coronary atherosclerosis, percutaneous coronary intervention

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Correspondence: Michelle Morris, Indiana University School of Medicine, 1800 N Capitol Ave, MPC2, ME-400, Indianapolis, IN 46032, US E: michynes@iu.edu

Development of atherosclerotic plaques is a long and complex process and many of the pathogenetic mechanisms are still not fully understood. While various stages of plaque growth and healing are involved, since the beginning of modern medicine 'hardening' of the coronary arteries has been recognised as a key feature of cardiovascular pathology.[1] Recently, coronary calcification has become a topic of growing interest as new modalities for calcium identification and modification during percutaneous coronary intervention (PCI) are being used. Atherosclerotic calcification is thought to be a response to vascular injury, inflammation and repair.[1] There is a growing need to understand the development of coronary calcification as well as to better characterise the different types and location of atherosclerotic calcification. Appreciation of the morphology of coronary calcifications will enable appropriate use of modern intravascular imaging technologies and calcium modifying tools during PCI.

Pathology: Developmental Timeline in Atherogenesis

Pathological Intimal Thickening

Pathological intimal thickening, sometimes called fatty streaks, is composed of two major components: a lipid pool located near the intimal-medial border and layers of smooth muscle cells. The lipid pool is characterised by extracellular lipid deposits and proteoglycans.[2] Calcification typically first develops within intimal thickening as microcalcifications or punctate calcification, which is thought to result from apoptosis of smooth muscle cells occurring in the intima.[3] These microcalcifications form at the border of this necrotic core, which first occur in a speckled pattern and later become fragmented.

Fibroatheroma

As macrophages infiltrate the lipid pool, metalloproteinases are deposited in the surrounding matrix, which leads to the eventual development of a necrotic core and formation of fibroatheroma.[2] Early fibroatheroma, similar to pathological intimal thickening, may contain punctate calcification. Late fibroatheroma typically contains larger volumes of acellular necrotic cores with little extracellular matrix that results from macrophage apoptosis and accumulation of free cholesterol.[2] Later fibroatheroma may or may not contain calcification, but when it is present, it typically occurs as calcium fragments.[4]

Thin-cap Fibroatheroma

As the necrotic core of the fibroatheroma expands through macrophages actively digesting collagen, the fibrous cap can thin.[5] A thin-cap fibroatheroma (TCFA) is classified by the presence of thin fibrous cap <65 µm in thickness containing a large necrotic core. TCFA may contain calcification, typically microcalcification or punctate when present, with possible intraplaque haemorrhage.[4] These are thought to be vulnerable plaques as they are most prone to plaque rupture when the thrombogenic core comes in contact with circulating blood.[5] TCFAs are known to represent the leading cause of acute MI.[6]

Plaque Erosion

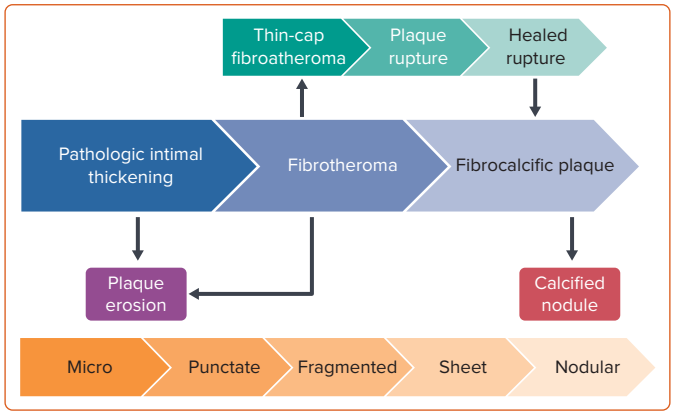
In contrast to plaque rupture, in plaque erosion, the fibrous cap is often thick, and while disrupted, remains intact. Plaque erosion can occur in the setting of both pathological intimal thickening and fibroatheroma. Most

Table 1: Classification of Calcium Based on Size and Appearance

Microcalcification	>0.5 µm and <15 µm
Punctate	>15 µm but <1 mm
Fragment	>1 mm
Sheet	>1 quadrant of the vessel circumference or 3 mm in circumferential diameter
Nodular calcification	Fractured calcium sheets with intact fibrous cap
Calcified nodule	Disruption of fibrous cap with luminal thrombus

Histopathology classification of calcification. Data source: Mori et al. 2018.[3]

Figure 1: Developmental Progression of Atherosclerotic Calcification



Schematic representation of the atherosclerotic disease progression from initial pathological intimal thickening to fibroatheroma and eventual development of calcified phenotypes of atherosclerosis; Morphological distribution patterns are noted in the lower bar. Data source: Mori et al. 2018.[3]

plaque erosion is not calcified, but if calcification is present it is generally fragmented.[2] Plaque erosion was previously thought to be present in approximately 20% of acute coronary syndrome (ACS) presentations, however with newer imaging techniques, this is thought to be an underestimate.[7] Plaque erosion has been seen more commonly in women and typically younger patients, and often presents as non-ST-elevation ACS.[8]

Healed Plaque Rupture and Fibrocalcific Plaques

Healed plaque is thought to result from plaque disruption. It may be detected by a ruptured fibrous cap or a 'buried' cap surrounded by a collagen-rich matrix.[3,4] Calcifications are typically greater in these lesions and out of proportion with the necrotic core. They typically accumulate in a fragmented way or in sheets.[4]

Morphology of Calcium Deposits

Calcification, when examined by light microscopy within atheromatous plaque, is classified based on its diameter. It begins with microcalcifications, which typically present within pathological intimal thickening and result from apoptosis of smooth muscle cells.[4] These microcalcifications can then coalesce into larger, punctate calcifications and eventually into calcium fragments within the necrotic core. The outer rim of the necrotic core calcifies first, with progressive calcium infiltration into the surrounding extracellular matrix. Sheets of calcium form as this infiltration extends and involves >1 quadrant of the vessel circumference or more than 3 mm.[3] Fragmented and sheet calcification are hallmarks of fibrocalcific plaque and healed ruptures.

Nodular calcification occurs when mechanical force causes fracture within the sheets of calcium. There is no intimal disruption present in nodular calcification despite fracture within the necrotic core. When disruption of the fibrous cap occurs with accompanied luminal thrombus, this is called a calcified nodule (CN).[2] CNs are the least common cause of acute coronary thrombosis, representing only about 5% of cases and exist only in highly calcified vessels (*Table 1*).[9]

Figure 1 demonstrates this progression of calcium distribution within atherosclerotic plaque as it advances from pathological intimal thickening into fibroatheroma.

Location of Calcification

Multiple processes are thought to be involved in the formation of arterial calcification. This is typically dependent on the location of the calcification as well as the layer of deposition.

Intima

Intimal calcification in the setting of atherosclerosis is associated with coronary disease progression. It is typically intimal calcification that is identified on coronary artery calcium scoring and an increasing burden is known to be associated with increased cardiovascular risk.[4] Risk for intimal calcification is typically increased by classic cardiovascular risk factors including age, hyperlipidaemia and diabetes. Yahagi et al. demonstrated a significant difference in the extent of coronary calcification that exists between people with uncontrolled diabetes (HbA_{1c} ≥12% [108 mmol/mol]) and those without diabetes. They demonstrated the presence of increasing calcification in lesions identified in patients with uncontrolled diabetes (*Figure 2*).[9]

Medial

Medial calcification, also known as Mönckeberg calcification, is most commonly found in the aorta and peripheral vessels and not typically in coronary arteries. It results from an accumulation of calcium phosphate in the form of hydroxyapatite crystals within the medial layer of the arterial wall. This process has been more commonly identified in patients with long-standing diabetes as well as chronic kidney disease.[4] The prevalence of medial calcification within the coronary arteries is not well known. With the use of intravascular ultrasound, isolated deep calcification – defined as calcium at the media/adventitia border or closer to the adventitia than to the lumen – was identified in 28% of native coronary lesions.[10] Medial calcification typically leads to loss of elasticity within the arterial wall.[3]

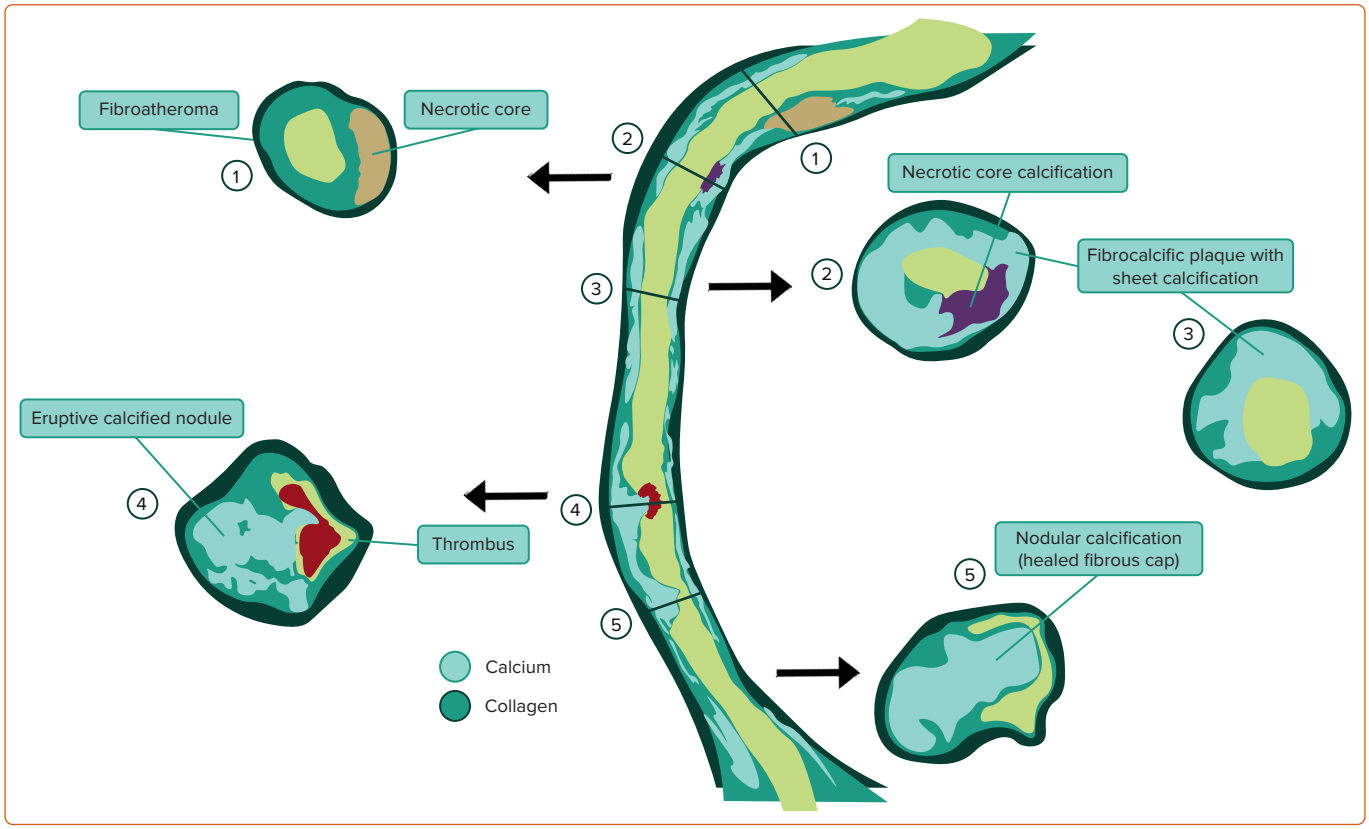
Adventitial Calcification

The adventitia has been increasingly recognised to be involved in the development of vascular inflammation and macrophages are deposited in the adventitia near the site of inflammatory atheromatous lesions.[11,12] While adventitial calcium is not well described, adventitial calcification results from fibroblasts, the primary cell type of the adventitia.[13] In animal models, adventitial fibroblasts have been shown to transform into phenotypic myofibroblasts or smooth muscle cells and participate in calcific lesion formation during vascular atherogenesis, while adventitial calcification has also been documented in human aortic tissue.[13]

Coronary Calcification Detected by CT

Coronary calcifications can be well demonstrated with the use of cardiac CT imaging. Coronary calcium screening is an established screening method to detect occult coronary artery disease due to the close link between the extent of coronary artery calcifications and subsequent

Figure 2: Morphological Types of Coronary Calcification



Graphic representation of examples of types of coronary calcification in the long axis of a vessel with cross-sectional reference points. Schematic colour representation for areas with predominant collagen (dark green) and calcium (turquoise blue). Necrotic core (non-calcified) is demonstrated (brown) with thin cap delineating it from vessel lumen (light green). Erosive calcified nodule with superimposed thrombus (red) occluding vessel lumen (light green).

cardiovascular events. Age- and sex-adjusted normalisation is now standard to detect premature establishment of coronary atherosclerosis, which is in turn closely linked to classic cardiovascular risk factors.[14] The method used by Agatston et al. to calculate a coronary calcium score (CCS) sums up all areas of calcification with thresholds for coronary artery calcification lesion detection based on >130 Hounsfield units and multiplies plaque density with area.[15] It does not specifically stratify scores based on density patterns or location proximally or distally in vessels, nor does it weigh risk based on coronary artery dominance (right versus left versus co-dominant). Increasing strata of CCS using the Agatston method have been epidemiologically linked with a graded increased risk of future major cardiovascular events, in particular, cardiovascular death and MI.[16–18] A calcium score of >400 Agatston units has been shown to be associated with worse clinical outcomes.[19]

Distribution Patterns

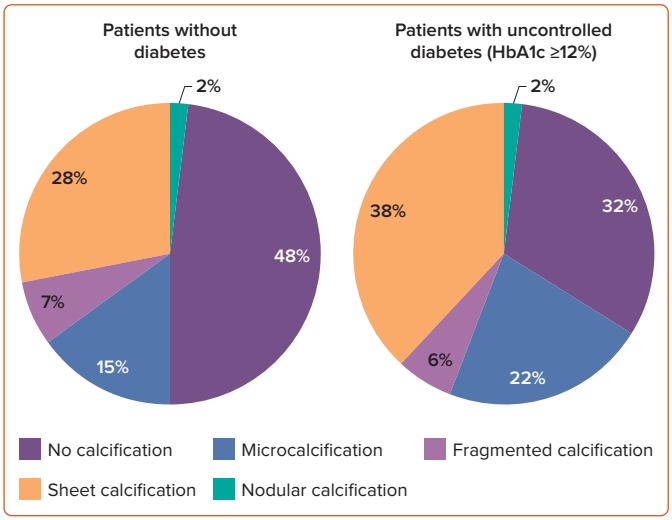
The variation in density of calcification and diffuseness can be quite variable and individuals with a similar CCS may have different risk levels for obstructive coronary disease based on the pattern of distribution.[20] While the classic method by Agatston used 3 mm slice thickness, more dense slicing patterns down to 1 mm were shown to significantly increase the sensitivity to detect coronary calcifications and may affect clinical risk calculations associated with a low CCS.[20] Diffuse disease as defined by the presence of more coronary territories with coronary calcification has been linked to increased risk of major adverse cardiovascular events (MACE). Ferencik et al. demonstrated that the presence of calcification in the proximal dominant vessel was independently associated with ~2.6-fold increased risk of MACE.[21] The presence of each additional vessel with calcification increased the risk of MACE by ~70% after adjustment for Framingham risk score and CCS category.[21] In the study by Foldyna et al., increasing calcium density was closely correlated to coronary artery calcification (CAC) volume, but less with an increasing number of coronary lesions. This was interpreted by the investigators to show that diffuse multi-segment coronary artery disease is linked to lower calcium density.[20] Coronary dominance (right dominant versus co-dominant versus left dominant) had no significant association with total CCS after multivariate adjustment.[22] Lesions of spherical morphology and pericardial location were associated with lower risk of MACE as were lower-density lesions.[23]

Coronary Calcification and Thrombosis

The specific mechanisms triggering acute MI in patients with coronary artery disease are complex and have been widely studied. Coronary calcification is an indicator of healed plaques but is also intrinsically linked to a higher likelihood of causing in situ thrombosis. Segments of coronary arteries with endothelial dysfunction have been shown to have evidence of plaque vulnerability, but also more extensive coronary calcifications.[24] Coronary endothelial dysfunction is associated with retention of osteogenic endothelial progenitor cells.[25]

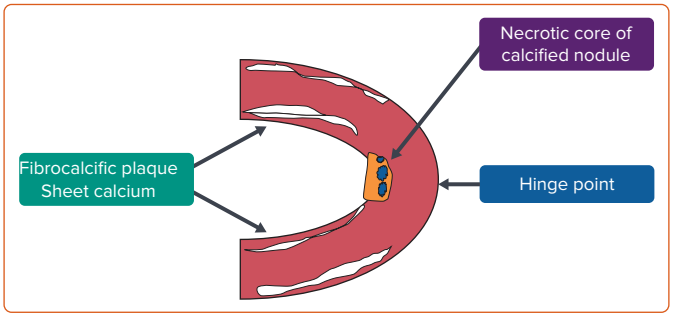
Elevated lipoprotein (a) is a strong emerging cardiovascular risk factor and closely linked to the emergence of particularly high CCS in middle-aged patients with elevated cardiovascular risk.[26] It has been postulated that lipoprotein (a) may interfere with fibrinolysis due to binding with fibrin and its pro-aggregatory effect on platelets has also been demonstrated.[27,28] Patients with elevated lipoprotein (a) have been shown to have an increased risk for arterial thrombotic events and a lower threshold for antiplatelet therapy is recommended for this group. From a lesion-specific

Figure 3: Representation of Prevalence of Coronary Calcification According to Absence or Presence of Uncontrolled Diabetes



Data source: Yahagi et al. 2017.[9]

Figure 4: Hinge Point of Calcified Nodule



Graphic representation of calcified nodule located at a 'hinge point' between areas of fibrocalcific disease with sheet calcification. This sheet calcification is stiff and less susceptible to mechanical forces relative to the calcified nodule which will have greater motion with the cardiac cycle, predisposing this to disruption of the fibrous cap. Data source: Torii et al. 2021.[29]

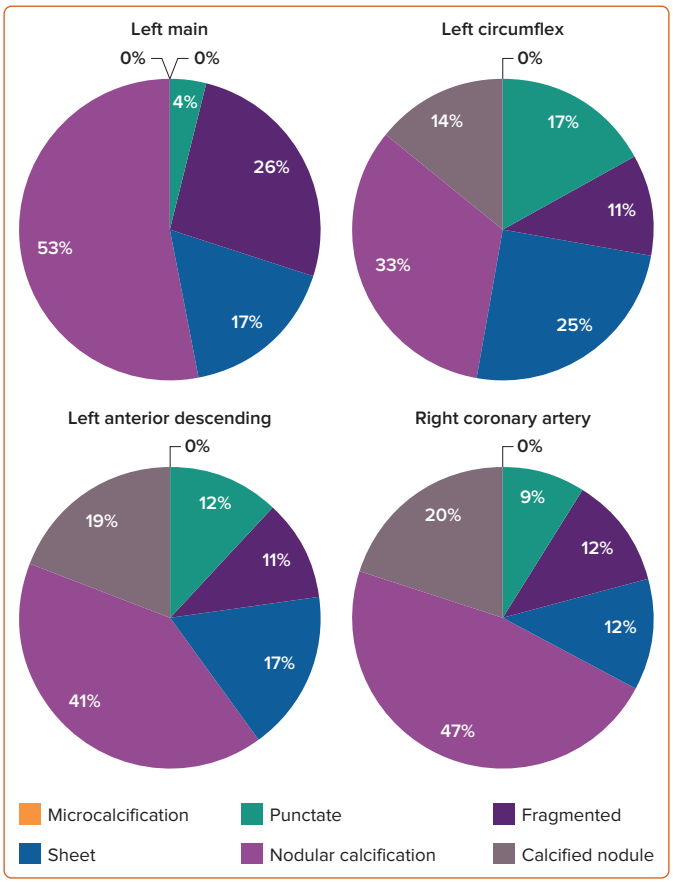
perspective, disruption of the protective intimal layer and reduction of the anti-aggregatory properties of normally functioning endothelium is a step that can lead to aggregation of platelets on the subintimal structure and initiation of coronary thrombus formation.[2,27] Not surprisingly, the presence of eruptive CNs has been linked to superimposed thrombus formation, acute coronary syndrome and sudden death (*Figure 3*).[29]

Association of Specific Types of Calcified Lesions with Thrombosis

The presence of significant coronary artery calcification detected with CT has been linked to an increased risk for MACE.[30] The degree of calcification, however, does not reliably correlate with plaque vulnerability. Based on autopsy studies, vulnerable plaques are typically TCFAs associated with large necrotic cores. These lesions typically show small calcifications (micro, punctate and fragmented). While the mechanism of plaque rupture has been debated, microcalcifications (>5 µm) have greater risk for plaque rupture which may be secondary to increased local sheer stress.[31]

Similarly, when assessed by intravascular ultrasound, culprit lesions with spotty calcification (defined by an arc of calcium <90) were most commonly found in acute MI.[32] Areas of severe calcification in the form

Figure 5: Variation of Coronary Calcification in Non-culprit Vessels



Data source: Torii et al. 2021.[29]

of sheet calcification or fibrocalcific plaque, while associated with higher plaque burden, are typically more stable.[2] An exception to this is a CN, which can be an important contributor to ACS presentation in older adults, particularly in patients aged over 65 years.[29]

Coronary-specific Calcification Patterns

While CNs represent the least common aetiology of acute MI, they are more commonly seen at the left main bifurcation as well as tortuous, heavily calcified right coronary arteries. Torii et al. hypothesised that these CNs, specifically within the proximal to mid-right coronary artery, are more likely to form at hinge points, or areas of increased motion within the cardiac cycle.[29] These hinge points are surrounded by areas of fibrocalcific plaque with sheet calcification making the surrounding vessel stiff and less susceptible to mechanical forces (*Figure 4*).[29] The increased frequency of CNs within the left main bifurcation is also likely to be determined by larger necrotic cores.[33] Similarly, Torii et al. examined the varying degrees of calcification within the coronary arteries (*Figure 5*).[29] They found that nodular calcification and CNs were more common in the left anterior descending and right coronary arteries, whereas sheet calcification was more common in circumflex vessels.[29]

Conclusion

While the presence of coronary calcification infers increased cardiac risk, understanding the spectrum of calcification is important to estimate the risk for thrombosis, as well as anticipating challenges with coronary vessel expansion and stent delivery during PCI. With the rapid development of sophisticated intra-arterial imaging methods, which include

intravascular ultrasound and optical coherence tomography, a much more granular impression of the various distribution patterns of coronary calcium has become possible. The presence of calcified sheets, nodular calcifications, eruptive calcified nodules, as well as non-calcified necrotic cores can be accurately determined using current technology, as well as the depth of calcium within the vessel structure. Knowledge about the types, morphology and distribution of coronary calcium is of increasing importance in contemporary complex PCI. ❑

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