The Impact of Coronary Artery Calcification on Long-Term Cardiovascular Outcomes

Noémi Mitra, Renáta Gerculy, Evelin Szabó, Diana Opincariu, Monica Chițu, Imre Benedek

Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Târgu Mureș, Romania

CORRESPONDENCE

Noémi Mitra

Str. 22 Decembrie 1989 nr. 76
540124 Târgu Mureș, Romania
Tel: +40 265 217 333
E-mail: mitranoemi@gmail.com

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Renáta Gerculy • Str. 22 Decembrie 1989 nr. 76,
540124 Târgu Mureș, Romania. Tel: +40 265 217 333,
E-mail: gerculy_renata@yahoo.com

Evelin Szabó • Str. 22 Decembrie 1989 nr. 76, 540124
Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail:
szaboevelin22@yahoo.com

Diana Opincariu • Str. 22 Decembrie 1989 nr. 76,
540124 Târgu Mureș, Romania. Tel: +40 265 217 333,
E-mail: diana.opincariu@yahoo.ro

Monica Chițu • Str. 22 Decembrie 1989 nr. 76, 540124
Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail:
iulia.chitu@yahoo.com

Imre Benedek • Str. 22 Decembrie 1989 nr. 76,
540124 Târgu Mureș, Romania. Tel: +40 265 217 333,
E-mail: imrebenedek@yahoo.com

ABSTRACT

Decades of research and experimental studies have investigated various strategies to prevent acute coronary events. However, significantly efficient preventive methods have not been developed and still remains a challenge to determine if a coronary atherosclerotic plaque will become vulnerable and unstable. This review aims to assess the significance of plaque vulnerability markers, more precisely the role of spotty calcifications in the development of major cardiac events, given that coronary calcification is a hallmark of atherosclerosis. Recent studies have suggested that microcalcifications, spotty calcifications, and the presence of the napkin-ring sign are predictive vulnerable plaque features, and their presence may cause plaque instability.

Keywords: coronary atherosclerosis, vulnerable plaque, unstable plaque, coronary calcification

INTRODUCTION

Cardiovascular diseases remain the leading cause of mortality worldwide despite recent major breakthroughs in invasive therapeutic procedures as well as in invasive and noninvasive diagnostic modalities. The mortality, morbidity, and socioeconomic influence of this disease makes its early diagnosis and prevention of the utmost importance.¹ The vast majority of cardiac deaths are from coronary artery disease (CAD), which is a complication of atherosclerosis, most often being represented by the rupture of an unstable coronary plaque.² Major advances in cardiovascular imaging made the assessment of coronary plaque characteristics possible. A vulnerable plaque is characterized by a build-up of lipids, fibrous tissue, and inflammation, and the presence of acute thrombosis. They can accumulate a few specific characteristics such as spotty calcifications, napkin-ring sign, positive remodeling, and low attenuation. Coronary computed tomography angiography (CCTA) has been proven as one of the most useful noninvasive imaging techniques assessing macrocalcifications, and it is useful predicting the global risk of acute events; however, it is not useful for identifying lesions prone to rupture. For the determination of plaque vulnerability and for the quantification of calcium within the plaque, intravascular ultrasound

(IVUS) or optical coherence tomography (OCT) are preferred. IVUS has high sensitivity and specificity for detecting dense calcific plaques and spotty calcifications. OCT can penetrate calcium and assess its other characteristics such as volume and thickness.^{3–8} In this review, we focus on coronary artery calcification and its role in advanced atherosclerosis, given that many imaging modalities have proposed spotty calcifications to be one of the predictors of plaque instability and of future cardiac events.⁵

IMAGING ATHEROSCLEROSIS AND VULNERABLE PLAQUE MORPHOLOGY

The prevention of major cardiac events is based on the identification of high-risk patients who may benefit from intensive preventive measures. Given that the majority of acute cardiovascular events is caused by the rupture of an unstable atherosclerotic plaque, the identification of these vulnerable coronary plaques is the main goal in prevention.^{9,10}

Atherosclerosis is a chronic inflammatory state that results in the calcification of lipid-loaded plaques.^{11,12} It begins with the accumulation of cholesterol and low-density lipoproteins in the sub-intimal region, causing irritation and inflammation, and attracting macrophages, which are trying to remove the lipoprotein complex. If the lesion continues to progress and not heal, a necrotic core will form with dying macrophages and with a rim of microcalcifications. That is why coronary artery calcification is a marker of atherosclerosis, developing as a healing response to local macrophage activity.^{13–15} When the cap of this atheroma reaches a critical thinness, it is more likely to rupture, hence the term ‘vulnerable plaque’, leading to thrombus formation and occlusion.^{13,16,17} Atherosclerotic lesions may be visualized via angiography, computed tomography (CT), CCTA, IVUS, or OCT, each providing different information. Characteristics associated with plaque instability are large plaque and necrotic core volume, thin-cap fibroatheroma (TCFA), napkin-ring sign, spotty calcification, low attenuation, positive vascular remodeling, and inflammation.^{8,13} Some of these can be identified by noninvasive imaging (CCTA), others, such as cap thickness, may be identified with invasive methods like OCT.¹⁸ Given that the size of microcalcifications and TCFA are below the CCTA scan spatial resolution, IVUS and OCT offer the possibility of plaque calcium quantification and arterial wall analysis.^{19,20} In recent years, noninvasive imaging concentrates not only on plaque morphology but also on disease activity in the lesions, using complex techniques called metabolic imaging. These novel method-

ologies provide insight into the underlying inflammation, detected with positron emission tomography (PET) and magnetic resonance (MR).²¹ Cardiac MR has the ability to identify some unstable plaque characteristics, based on uptake of gadolinium-based contrast associated with macrophage accumulation and hemorrhage within the plaque. The future of plaque imaging may be expanded by the recently developed hybrid scanners, which offer simultaneous metabolic and morphology imaging.^{22,23}

IMAGING CALCIUM DEPOSITS

Macroscopic vascular calcium deposits can be detected by CT angiography which has high sensitivity and specificity for detecting significant lumen stenosis. The assessment and quantification of calcium deposits is possible using the coronary artery calcification score (CAC scoring), a good marker of overall coronary plaque burden, which is also used to predict future coronary events. However, it is not as useful in describing vulnerable lesions, as recent studies have shown that the CAC score is a direct predictor of coronary artery disease, but it is inversely associated with acute coronary events.^{24–26} The assessment of spotty calcifications may be possible using IVUS and OCT. IVUS provides high sensitivity and specificity in detecting large dense calcified lesions; however, its assessment is limited to arc and length.²⁷ OCT is able to penetrate calcium and assess its qualities, and it is also capable of quantifying macrophages, providing information about the level of plaque inflammation. OCT can provide information on morphological as well as disease activity characteristics that are equivalent to a histological examination, making the identification of higher risk patients more accessible.^{28,29}

CORONARY ARTERY CALCIFICATION

Coronary artery calcium presents a broad spectrum of shapes and sizes with regular or irregular borders. The deposits appear in different locations, and as suggested in recently published studies, these characteristics have a very important prognostic value.³⁰

The extent of calcium in coronary arteries has different clinical implications. Traditionally, calcified plaques had been viewed as stable atheromas, but with the development of imaging technologies this view has evolved.³¹ Based on the location of the calcium deposits we can differentiate between medial Mönckenberg calcification (often seen in old patients with diabetes and renal failure), intimal calcification (more common in atherosclerosis), and infantile calcification.

MICROCALCIFICATIONS

Microcalcifications may represent an early, active stage in plaque calcification. They grow into larger masses and extend from deep within the necrotic core, forming a calcified sheet at the end.³² The visualization of microcalcification may be possible with 18F-sodium fluoride (18F-NaF) PET imaging, which could help to identify active microcalcifications, because it accumulates in macrophages due to their high demand for glucose. An association between 18F-NaF-positive plaques and high-risk plaques has been demonstrated.³³ A few studies have investigated microcalcifications with the help of OCT and demonstrated to be related to mild stenosis with extensive inflammation and a large necrotic core.³⁴ Studies have shown that on a cellular level microcalcification may play a role in stress concentration (this effect is independent of size and location) and rupture of the plaque, because if two microcalcifications are located close to each other the stress concentration rises, and a whole region is exposed to high stress (high background stress being TCFA and cap shoulders).^{35,36}

SPOTTY CALCIFICATIONS

Spotty calcifications are small calcium deposits, in the range of 1–3 mm, some of them showing progressive calcification, turning into end-stage macroscopic calcifications.^{37–39} In general, there are two explanations for the presence of spotty calcification.⁴⁰ It is mostly associated with unstable plaques with more extensive atherosclerosis and accelerated disease progression, playing an important role in plaque destabilization, or merely indicating the presence of an unstable plaque.⁴¹ Recent studies found that spotty calcifications were more often found in fibroatheromas and more frequently present in ruptured plaques. Furthermore, culprit lesions in acute myocardial infarction were characterized by spotty calcifications, more often than in stable angina pectoris.⁴²

Spotty calcifications show greater inflammation and may provoke greater pro-inflammatory factor expression, followed by macrophage-derived cytokine expression and vascular smooth muscle mineralization.

LARGE CALCIFICATION

Extensive calcification or end-stage calcification is irreversible and may be more strongly associated with stable fibrotic plaques, increased mineralization, and limited inflammation, but the relationship between coronary ar-

tery calcification and plaque stability is not yet fully understood.^{24,43,44} However, the CAC score is an independent predictor of major cardiac events, and calcified atherosclerosis in other vascular beds is associated with the risk of mortality.^{45–47}

Several studies conducted in the last 10 years offer contradicting results. Plaque calcification, including volume and area, can be higher in asymptomatic patients. Other studies found that calcification volume is higher in patients with stroke, and a larger plaque may be associated with higher intraplaque hemorrhage.⁴⁸

A study published in 2019, which followed patients with no previous coronary artery disease for 10 years after CCTA investigation, reported that the presence of spotty calcifications and napkin-ring sign provides prognostic value, allowing for better risk stratification. In addition, a long-term CT angiography study demonstrated that a vulnerable plaque has to continue to gather large necrotic core volumes to sustain plaque instability, because as previous observations have proven, a large percentage of the lesions identified as vulnerable at baseline diagnosis had stabilized over the following year.^{13,49}

ASSOCIATION BETWEEN CALCIFICATION NUMBER AND LOCATION AND PLAQUE VULNERABILITY

Atherosclerosis and calcification is an organized process, characterized by an irreversible and continuous build-up of plaque within the arterial wall.⁵⁰ Cardiac MR studies have classified lesions into single and multiple calcifications. Studies show that multiple calcifications are strongly associated with intraplaque hemorrhage and ulceration, making them more vulnerable. In addition, they may provoke a more activated inflammatory response, increasing the possibility of plaque rupture.^{51,52} The increasing number of spotty calcifications shows a strong correlation with the incidence of ruptured plaques. The number of calcifications is higher in acute myocardial infarction and unstable angina, proving that multiple calcifications may lead to higher stress concentration and plaque rupture.⁵³

A study exploring the spatial distribution of atherosclerosis and coronary artery flow patterns found that coronary plaques develop mainly at bifurcations and on the inner walls of curved coronary segments.^{30,54} Several studies described a strong association between unstable lesions and calcium location, and an association between superficial calcification (calcium located closer to the lumen than to the adventitia) and plaque vulnerability has been dem-

onstrated. On the other hand, calcification located closer to the media-adventitia, away from the lumen, showed a higher risk for in-plaque hemorrhage but no impact on plaque destabilization.^{52,55,56} A research group used OCT imaging to assess superficial calcium deposits and found no significant association with symptomatic plaques; however, sheet-like superficial calcium plates were present in a significant percentage at the culprit lesion site.⁵⁷ A study published in 2016 in Japan has enrolled approximately 100 patients with acute coronary syndrome who underwent OCT imaging of the culprit lesion, dividing them into two groups based on the presence of plaque rupture.⁵⁸ The study concluded that spotty calcifications were present more frequently in the group with plaque rupture. Also, these were smaller in size with shallow displacement, compared with the non-ruptured plaque. The study indicated that spotty calcifications may serve as an independent predictor of plaque rupture.^{59–62}

A study published in 2020 assessed the correlation between features of plaque instability, calcification patterns and coronary artery disease, using CT angiography. The study concluded that large calcifications or denser lesions are associated with a higher stenosis and CAC score, and with lower plaque instability. The lesions with spotty calcifications had lower calcium score with lesser lumen stenosis and high instability score.⁶³ Furthermore, plaques with mixed calcification showed similar characteristics to the large calcification patterns, but the plaque instability score was closer to the average of those with spotty calcification. Another interesting observation was that spotty calcification with low density was mostly associated with low attenuation and napkin-ring sign, whereas large calcifications were present together with higher density and positive remodeling. The finding supports the theory that coronary artery events mainly result from the rupture of a mildly stenotic plaque, questioning the significance of the CAC score as a significant predictor of future events.⁶⁴ These recently published results are consistent with previous studies examining plaque calcification patterns, proving calcification is a good predictor of future coronary artery disease events. In accordance with previous evidence, we can conclude that spotty calcification is more frequently associated with the culprit lesion and plaque progression and instability, with a lower grade of coronary stenosis.

CONCLUSION

Calcification is an important component of atherosclerosis. There is a proven correlation between calcification

and plaque progression and stability. Spotty calcifications may correlate with inflammation and instability, and may represent the active stage of vascular calcification. Plaque rupture is known to be the main cause of acute coronary syndromes. Therefore, its prediction is very important in the clinical setting, and identification of spotty calcifications in an atheromatous plaque at CCTA examination may indicate a higher degree of vulnerability.

CONFLICT OF INTEREST

Nothing to declare.

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