

The Napkin Ring Sign – the Story Behind Invasive Coronary Angiography

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ABSTRACT

Coronary artery disease (CAD) represents one of the leading cause of morbidity and mortality across Europe. Most of the patients do not experience any warning sign before the coronary event develop, therefore screening this group of patients is essential to prevent major cardiac events. Coronary computed tomography angiography (CCTA) offers a noninvasive approach of the coronary arteries, providing information not only on the presence and the severity of the coronary stenosis, but also being able to characterize the coronary wall structure. CCTA allows complex evaluation of the extension of CAD, and by assessing the atherosclerotic plaque structure can identify its vulnerability degree. The napkin-ring sign (NRS) represents a ring-like attenuation of the non-calcified portion of the coronary lesion and has a high specificity (96–100%) for the identification of thin cap fibroatheroma (TCFA) or culprit lesion in acute coronary syndromes (ACS). It is also an independent predictor for ACS events and the strongest predictor for future ACS. Modern CCTA can provide submillimeter isotropic spatial resolution. Thus, the CT attenuation based tissue interpretation enables the assessment of total coronary plaque burden, and individual plaque components, with a similar accuracy as IVUS based investigations. This review aims to present the important role of CCTA, as a potent screening tool for patients with CAD, and the current evidences in the detection and quantification of vulnerable plaques.

Keywords: cardiovascular diseases, napkin-ring sign, culprit lesion, vulnerable plaque

INTRODUCTION

Cardiovascular disease (CVD) is still one of the leading cause of morbidity and mortality in Europe. Annually, it represents approximately 4 million deaths due to CVD across the continent. The population of Eastern Europe is more likely to be affected by CVD, especially by coronary artery disease (CAD), which could progress to an acute coronary syndrome (ACS) turnout in myocardial infarction or unstable angina.¹ Atherosclerosis is a chronic inflammatory process, developing macro and microstructural modifications of the artery wall, resulting in CVD. Lipid accumulation in the arterial intima, inflammation (local inflammatory reaction and macrophage infiltration of the affected arterial segment), foam cell formation, muscle cell proliferation, necrosis, calcification and arterial wall fibrosis induce important functional and morphological changes, and lead to plaque

formation, resulting in CAD.² Progression of the CAD varies among patients, but generally it takes a long period of time until the first clinical manifestation of the disease appears.³ The most common and dramatic manifestation of CAD is related to plaque rupture or erosion, followed by the activation of the coagulation cascade subsequently intraluminal thrombosis. In a significant part of the cases, the first manifestation of the CAD is acute myocardial infarction (AMI) or sudden cardiac death (in 50% of men and 64% of women).⁴ Therefore most of the patients presented with ACS do not experience any symptoms or warning signs before the coronary event occurs. There are several methods to evaluate patients with stable chest pain. Coronary computed tomography angiography (CCTA) offers a noninvasive approach of the coronary arteries, being recommended as a screening tool, especially for patients with low to intermediate risk of CAD.⁵ Conventional/Invasive coronary angiography – ICA (considered the gold standard for the diagnosis of significant CAD) has a high specificity and sensibility to assess the obstructive lesions but unable to characterize the plaque structure, or to identify the high risk plaques, although it was demonstrated by several studies that a notable proportion of acute coronary events occur due to the rupture of mildly stenotic plaques.^{6,7} Compared to conventional coronarography, CCTA can provide prognostic information from non-obstructive lesions by identifying the vulnerable plaque parameters, like Napkin-ring sign, low attenuation, spotty calcification and positive remodeling of the vessel. Moreover, non-contrast CT scans can assess epicardial adipose tissue (EAT) and by quantifying coronary artery calcification, using a score system (Agatson score) can predict plaque progression and future coronary events beyond traditional risk factors.^{8,9}

BEYOND THE CORONARY PLAQUE MORPHOLOGY

Plaque rupture, followed by an acute coronary syndrome (ACS) has been related to the rupture or erosion of a vulnerable plaque with lipid rich necrotic core and a thin fibrous cap, followed by acute thrombosis and subsequently coronary occlusion.^{7,10}

Currently there are six types of atherosclerotic lesions, defined by the American Heart Association (AHA). Type I – initial lesion, characterized by intimal thickening and smooth muscle cell accumulation in the intima. Type II – “Fatty streak” with luminal accumulation of foam cells, it usually regresses. Type III lesion – Preatheroma or progressive atherosclerotic lesion with extracellular lipid accumulation and pathologic intimal thickening. Type IV

lesion – Atheroma. Type V lesion – fibroatheroma, with thin fibrous cap, infiltrated by macrophages and lymphocytes, with the presence of a necrotic core. Type VI lesion – complicated plaque, without intact plaque surface and/or hematoma/hemorrhage and/or thrombotic deposit.¹¹ Based on the AHA classification, type I and type II plaque are reversible, capable to regress or to progress. Type III lesions are considered the precursors of the fibroatheroma, described by pathological structural changes such as an escalated amounts of lipids and multiple smooth muscle cell layers near the lumen. These “proatheromas” are infiltrated with a great number of foam cells. Interestingly, 40% of these cells originate from smooth muscle cells, and 60% from macrophages.^{12,13} Progression of deep intimal thickening to pathologic intimal thickening depends on a complex interaction between retention and oxidation of lipids and smooth muscle cell proliferation and inflammation respectively.¹³ Type IV lesions represent the first stage of advanced plaques, characterized by the appearance of the fibrous cap (containing collagen and proteoglycans, smooth muscle cells, macrophages and lymphocytes), framing the necrotic core (with large extent of lipids, originated from extracellular lipid pools and insufficient efferocytosis of dead smooth muscle cells and macrophages). The evolved foam cells in this region will be damaged (mostly by apoptosis) subsequently releasing further inflammatory material.^{14,15} From this stage of lesions, they can cause significant luminal narrowing, and can progress to complicated plaque with surface erosion, thrombosis, and calcification. Based on the thickness of the fibrous cap, they are less or more prone to complication. Numerous studies showed that the fibrous cap thickness (TCAP) offers one of the best markers for vulnerable plaques, between 54–84 μm of cap thickness being considered as a vulnerable, high risk plaque.¹⁶ Postmortem assessment of coronary arteries by examination of coronary cross section layers, showed that 95% of ruptured plaques had a thickness of the fibrous cap lower than 65 μm .¹⁷ Optical coherence tomography (OCT) examination in patients with ACS, determined a median cap thickness of 80 μm in non-ruptured plaques.¹⁶ Without an intact fibrous cap, the lipid-rich necrotic core can intercourse with the blood flow, facilitating the platelet accumulation and thrombus formation in the affected segments. The histopathological partition distinguished three types of lesions prone to provoke acute coronary events: rupture, erosion and calcified nodule.¹⁸

Ruptured plaques are characterized by a lipid-rich necrotic core, surrounded by a thin, fibrous cap with active inflammation. In most cases, the appearance of luminal thrombosis is caused by plaque rupture (approximately

60–70%), the rest of the cases resulting from plaque erosion, and about 5% being caused by thrombus formation at the level of calcified nodules.¹⁹ Plaque erosion is defined by a relatively intact intima, without cap disruption, where the blood flow comes into direct contact with intimal surface due to lack of endothelial cells, favoring thrombus formation.²⁰ Interestingly, autopsies revealed that a remarkable part of the thrombi in erosion (more than 85%) showed evidence of healing process (acute inflammatory cell lysis, invasion by smooth muscle cells, organized layers of smooth muscle cells, proteoglycans with varying degree of platelet/fibrin layering). On the other side, healing process was observed only in half of the ruptured plaques.²¹ The examination of coronary cross sections has suggested that repeated plaque ruptures can initiate further plaque progression.²²

The extension of the necrotic core also correlates with plaque complication. As the necrotic core extends outwards, causing thickening of the fibrous cap, concomitantly smooth muscle cells are depleted from the fibrous cap through cell apoptosis, therefore the cap thickness decreases.^{23,24} Simultaneously with the plaque progression, the vasa vasorum infiltrates the lesion and becomes leaky, provoking intraplaque hemorrhage.²⁵ The number of smooth muscle cells is inversely correlated with the progression of the atheroma, because of the migration and cell apoptosis.²⁶ There are numerous factors that induce smooth muscle cell apoptosis, thus the progressive cell loss contribution in plaque stability is more complex, and strongly affects the local milieu.^{27,28} This milieu in atherosclerotic lesions inhibits the phagocytosis, and defective efferocytosis of apoptotic cells, followed by secondary necrosis and leakage of intracellular contents, maintaining and exacerbating the inflammatory milieu.²⁹

In conclusion, there are several morphological and functional changes that lead to the progression of a preatheroma to a vulnerable plaque. Vulnerable plaques prone to rupture contain a large necrotic core, active inflammation and macrophage infiltration, thin fibrous cap, and numerous vasa vasorum at the affected level.³⁰ The mechanism of the rupture of a thin cap fibroatheroma are unclarified yet. Increased proteolytic activity, mechanical stress, and microcalcification of the fibrous cap are considered as relevant factors.^{31–34}

CAN WE PREVENT ACUTE MYOCARDIAL INFARCTION BY SCREENING FOR CORONARY ARTERY DISEASE?

Prevention of acute coronary events seems to be the only potent strategy to reduce the rate of MACE and improve

mortality and morbidity.³⁵ Although major efforts are ongoing to predict which plaque will cause MACE on an individual plaque level. Currently the diagnostic strategies targets the detection of myocardial ischemia and haemodynamically significant luminal narrowing plaques, but ignores the huge issue of a MACE occurring as the first (half of the individuals) and the only manifestation of CAD.

Based on the morphological characteristics of the fibroatheroma, there are several imagistic features to identify vulnerable plaques. The rapid progression and development of cardiovascular imaging technologies in the recent decades allows to introduce in clinical practice screening imagistic procedures for primary prevention, or assessment of the extension of CAD, which could be useful to detect vulnerable lesions. Although these major developments of imagistic techniques, identifying vulnerable plaques remain a major challenge. Early diagnosis of CAD could promote physicians to initiate complex treatment for adequate primary prevention, thus reducing the incidence of acute coronary events.³⁶ There are several imagistic methods to assess the coronary vessels, invasive coronary angiography (ICA) was considered the gold standard for the diagnosis of coronary artery disease (both stable CAD and ACS).³⁷ Although ICA can describe the anatomy of the coronary vessels and quantify the lumen narrowing stenosis, it does not provide information about the coronary vessel wall structure, or the atherosclerotic plaque composition, therefore being unable to identify the vulnerable plaques.³⁸ Additional invasive imagistic methods could be used for a better evaluation of the extension of CAD and to identify the presence of a rupture prone plaque. OCT can provide very high resolution (10–20 μm) images, capable for a microscopic characterization of plaque morphology, therefore can be used to evaluate plaque vulnerability, by measuring the thickness of the fibrous cap, and to detect lipid content, moreover only OCT can detect the eroded plaques.³⁹

Intravascular ultrasound (IVUS) represents another invasive intravascular imagistic technique to improve the diagnostic accuracy of ICA. IVUS could be used for measuring the lumen area, plaque burden, and vascular remodeling. IVUS-based studies identified several imagistic biomarkers in association with plaque vulnerability, like the presence of an extensive necrotic core surrounded by a thin fibrous cap, with dense macrophage infiltration; large lipid pool, spotty calcification and positive vascular remodeling.^{40,41} Spectroscopy, thermography, angioscopy and intravascular cardiac MRI also represent invasive imagistic methods, which could be used for providing additional information, like plaque temperature, plaque inflammation and neoangiogenesis.

Although the previously presented invasive imagistic markers could describe and identify precisely the high risk atherosclerotic plaques, they cannot be used as a screening method for primary preventions in a large population. Patel *et al.* found that, among 398,978 elective invasive coronary angiography, only 38% of the cases were positive for obstructive CAD, 62% of the patients had no obstructive disease, and 39% had normal coronary arteries.⁴² Cardiac CCTA offers a non-invasive approach for CAD patients, and can be used as a “gatekeeper” to reduce unnecessary invasive diagnostic procedures. Using at least 64-slice multidetector row has a sensibility of 98% and a specificity of 90%, because of the elevated sensitivity, the negative predictive value of the CCTA investigations had a 95 to 100% to rule out obstructive CAD, and an excellent negative predictive value for future events.⁴³ Multidetector computed tomography (MDCT) has a capability to describe and localize accurately the lumen narrowing atherosclerotic plaques, by measuring local tissue attenuation can assess the morphology and the composition of these lesions and having a high temporal and spatial resolution. Moreover in the guidelines for the diagnosis and management of chronic coronary syndrome published by the European Society of Cardiology, computed tomography angiography has a class I recommendation for diagnosing CAD in symptomatic patients.⁴⁴ Contrast-enhanced ultrasonography and high resolution magnetic resonance imaging are also non-invasive investigations to characterize the coronary lesions, within their benefits and limits.

Modern multislice computed tomography with increased spatial resolution permits a more complex characterization of non-calcified coronary plaques (defined as <130 Hounsfield units), like positive remodeling, low attenuation plaque and spotty calcification.⁴⁵ Moreover, on CCTA provided images several authors described a ring-like attenuation of the non-calcified portion of the coronary lesion, which was termed the Napkin-ring sign.^{46,47} Thus, the non-calcified plaques are categorized in three different classes: homogenous plaque, non-napkin-ring sign heterogenous plaques and napkin-ring sign heterogenous plaques.⁴⁸ The napkin-ring sign on CCTA provided images represents a large necrotic core – low attenuation core, surrounded by a thin-cap fibroatheroma – rim like thin area of higher attenuation. Histopathological analysis on ex vivo donor heart demonstrated the correspondence between the napkin-ring sign and the presence of the histological markers of a vulnerable plaque at that sequence.⁴⁹ Based on recent studies, near the napkin-ring sign only fibrofatty plaque features were independent predictors for

future MACE, and have been associated with events in short- and mid-term outcome periods.^{50–52}

THE NAPKIN RING SIGN

As we mentioned before, histopathological analysis of culprit and non-culprit TCFAs with identical luminal narrowing effect found that only fibrous cap thickness and necrotic core size are independent predictors of plaque rupture.⁵³ Furthermore a large necrotic core cross sectional area, and the presence of macrophage infiltration are the best discriminators between ruptured plaque or TCFAs and stable atherosclerotic lesion.¹⁰ Moreover, 80% of the vulnerable plaques prone to rupture, the necrotic core area is >1 mm².⁵⁴ Modern CCTA can provide submillimeter isotropic spatial resolution, thus the CT attenuation based tissue interpretation enable the assessment of total coronary plaque burden, and individual plaque components, with a similar accuracy as IVUS based investigations.^{7,55}

A ring like CT attenuation pattern of non-calcified plaque was present in ACS culprit lesions and in plaques associated with slow-flow or no-reflow phenomenon during ICA.^{56,57} There are two major qualitative components in the CT provided images of a vulnerable non-calcified plaque which fulfill the criteria of a NRS: a center area of low CT attenuation tissue, apparently in contact with the lumen, and a higher attenuation plaque segment surrounding this central area (fibrous plaque tissue).^{48,49,58} The necrotic core area represent an important factor compared with non-NRS plaques, the necrotic core can be over twice the size in NRS plaques (median 1.1 mm² versus 0.46 mm²).⁵⁸ Interestingly the majority of these high risk lesions have necrotic core area over 1.0 mm².³⁰ Based on the CT images, the specificity of an NRS for a vulnerable atherosclerotic lesion and TCFA is exceptional (98% and 94.1%), but unfortunately the specificity of the NRS is relatively low.^{48,59} In clinical investigations the NRS had a high specificity (96–100%) for the identification of TCFA or culprit ACS, being also an independent predictor for ACS events.^{46,60} They also found that, the NRS was more frequent in TCFA compared with non-TCFA plaques (controlled by OCT).⁵⁶ Otsuka *et al.* found that the presence of NRS was the strongest predictor for future ACS [HR 5.55; 95% confidence interval (CI) 2.10–14.70, p <0.001], independent of other high-risk criteria.⁴⁶ Furthermore, a long-term follow-up study of 7.8 years, in a group of patients with CAD (including low-to-intermediate risk) evidenced an increased prevalence of NRS in patients with adverse events (63.4% vs. 2.8%, p <0.001). Moreover, the

NRS was the most important predictor of adverse events after assessment of the conventional risk factors, stenosis severity and plaque type.⁶¹

THE POTENTIAL UTILITY OF CCTA AND THE CLINICAL IMPLICATION OF NAPKIN-RING SIGN

The constant upgrade of MSCT technology, and new software features allow us a more complex and detailed non-invasive plaque characterization, using morphological and functional data (CT-FFR and ESS). Combining morphological and functional characteristics of the atherosclerotic plaque results in a highly accurate detection of the vulnerable and stable lesions. This new feature has established the CCTA provided coronary assessment as a first line investigation in patients with low to intermediate risk of CAD.^{44,62} In addition, the presence of inflammation at the coronary lesion could favor the atherosclerotic process. Recently by a complex assessment of the perivascular adipose tissue, CCTA has been proposed as an effective tool for quantification of coronary inflammation, which could be an important factor—besides the morphological and functional assessment of the coronary plaque—for an individualized coronary risk stratification.^{63,64}

Using CCTA as a potential screening tool for low-to-intermediate risk of CAD could reduce significantly the unnecessary ICA, moreover CCTA has an excellent negative predictive value, could be a good alternative to rule out the presence of CAD when pretest probability is intermediate.⁶⁵ The Prospective Multicenter Imaging Study for Evaluation of Chest Pain Study compared the presence of CAD in patients with typical symptoms, evaluated with CCTA versus functional testing, the rate of non-oCAD was 28% and 52% in the CCTA and functional testing group, respectively.⁶⁶ Despite the availability of CCTA or functional testing, up to 45% of patients are directly referred for ICA without prior functional testing.⁶⁷ It is important to be mentioned, although the technological improvement and the widely used radial access reduced the complication rate of ICA, still approximately 0.6–4.2% of the procedures have different type of complications.⁶⁸

Based on the previously cited studies, CCTA can provide accurate characterization of the coronary arteries, by detecting the obstructive plaques, and by the ability to visualize the coronary artery wall, could be used to assess the plaque morphology. Thus, assessing the cardiovascular system with CCTA, the acquisitioned images help to identify the high risk plaques, and by using a non-invasive imagistic method the physician could initiate the adequate treatment. Moreover, CCTA may help to identify coronary artery le-

sion progression or regression, providing a good feedback and control of the chosen therapy.^{69,70} Although it is not possible to control the therapeutic efficiency of a chosen intervention on the atherosclerotic plaque, repeated CCTA examinations, with the direct monitorization of plaque progression may lead to a superior therapeutic modulation.⁷¹

Another revolutionary perspective of CCTA is the use of radiomics, which means a process of extracting numerous quantitative features from the investigated region to create large data sets in which each abnormality is described by hundreds of parameters. The applicability of these features is still at an early stage, but the rapid progress encountered in the field of AI will probably bring major changes in the way we integrate clinical, biological, and imaging information, for a complex, individualized risk stratification and therapeutic decision-making.⁷²

CONCLUSION

The evolution and the rapid progression of CT imagistic technologies has changed the therapeutic approach of patients with suspected CAD, offering an early and accurate assessment of the coronary arteries. Due to the capability of CCTA to identify multiple high risk features of atherosclerotic plaques, such as the napkin-ring sign, positive remodeling, low CT attenuation, low endothelial shear stress and spotty calcification, this modern imaging technique may improve clinical evolution and lead to a more effective management of the cardiovascular patient.

CONFLICT OF INTEREST

Nothing to declare.

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