

# Noninvasive Imaging Biomarkers of Vulnerable Coronary Plaques – a Clinical Update

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## ABSTRACT

Atherosclerosis is a slow, progressive disease, with its most common manifestation and most severe consequences being coronary artery disease, which is one of the main causes of mortality and morbidity worldwide. The vast majority of cardiovascular deaths are caused by complications of atherosclerosis, most often being represented by the rupture of an unstable coronary plaque, regularly triggered by inflammation. A vulnerable plaque is characterized by a large, lipid rich necrotic core, a thin fibrous cap with macrophage infiltration, and the presence of multiple specific biomarkers such as positive remodeling, irregular calcifications, and low attenuation visible with coronary computed tomography angiography (CCTA). Identifying biomarkers that could predict the risk of plaque rupture with high accuracy would be a significant advance in predicting acute cardiac events in asymptomatic patients, furthermore guiding treatment of patients with this disease. The main indication of noninvasive imaging is to identify patients at risk based on the presence or absence of symptoms that can be related to myocardial ischemia. The diagnostic objective is to confirm or to exclude the presence of coronary plaques. Coronary imaging in asymptomatic individuals is used to estimate the risk of future cardiac events through the identification of non-obstructive high-risk plaques. The possibility to monitor the evolution of vulnerable plaques via noninvasive imaging techniques, prior to the occurrence of an acute clinical event is the main goal in plaque imaging. This manuscript will be focusing on recent advances of noninvasive imaging of vulnerable coronary plaques.

**Keywords:** vulnerable plaques, coronary CT angiography, noninvasive plaque imaging

## INTRODUCTION

Atherosclerosis is a slow, progressive disease that could lead to atheromatous plaque formation, causing luminal narrowing of the arteries. In most severe cases, plaques can rupture leading to coronary thrombosis, that obstruct blood flow to the heart. Atherosclerosis leads to plaque formation through inflammation, necrosis, fibrosis and calcification.<sup>1</sup> The most common manifestation and

most severe consequences of atherosclerosis is coronary artery disease, that includes stable angina as well as acute coronary syndromes, making the cardiovascular diseases one of the main causes of mortality and morbidity worldwide.<sup>2</sup> Given that it is projected to remain the leading cause of mortality, prevention strategies seem to be the only effective approach to reduce the incidence of this disease, improve mortality and morbidity, and reduce healthcare costs.<sup>3,4</sup> Acute coronary syndromes represent the most severe outcome of atherosclerosis. The vast majority of cardiovascular deaths are caused by complications of atherosclerosis, most often being represented by the rupture of an unstable coronary plaque.<sup>5,6</sup> Plaque destabilization is a complex biomechanical process that results from the cumulative effect of applied hemodynamical stresses, structural features, and biological processes that determine mechanical strength.<sup>7,8</sup>

## **THE CONCEPT OF VULNERABLE PLAQUE – MARKERS OF PLAQUE VULNERABILITY**

Acute coronary syndromes such as myocardial infarction and unstable angina, in most cases, are caused by a thrombus formed on an atherosclerotic plaque, plaque rupture being the base of fatal heart attacks in more than 75% of the cases.<sup>6,9,10</sup> A growing mass termed as a plaque is a buildup of lipids, fibrous tissue and inflammation.<sup>11</sup> An atherosclerotic coronary plaque is vulnerable if it has a high risk of thrombosis in a short term of time and fast progression of stenosis.<sup>9,12</sup> Researches are showing that many patients with acute cardiovascular events do not have severely narrowed arteries, while in the contrary, vulnerable plaques may show an eccentric deposit, buried in the artery wall, without blocking the blood flow through the artery. Therefore, severely stenotic coronary plaques do not always cause an acute major cardiac event. A vulnerable plaque is characterized by a large, lipid rich necrotic core, a thin fibrous cap with macrophage infiltration, and the presence of multiple specific biomarkers such as positive remodeling, irregular calcifications, and low attenuation visible with computed tomography angiography (CCTA).<sup>5,6,13,14</sup> Lipoproteins are contained within the intima, and seems to attract macrophages that secrete proteolytic enzymes that leave behind a soft and destabilized lipid-rich cavity, showing that inflammation has an important role in vulnerable plaque development.<sup>15</sup> If inflammation is associated with other factors, such as high blood pressure, it can lead to the cracking of the thin cap, causing spilling the contents of the vulnerable plaque into the bloodstream, causing the platelets to clump together and create a clot large enough

to block an artery. The presence of a necrotic core is indispensable in plaque rupture, without it there is no overlying fibrous cap to rupture. At the same time, a larger necrotic core has a higher risk of rupture than a smaller one.<sup>11,16,17</sup> Studies have also found that vulnerable plaques are filled with various cell types that stimulates blood clotting. Vulnerable plaques can be divided into two groups: rupture-prone and erosion-prone.<sup>11</sup> The term plaque erosion is used when even with microscopic search no plaque rupture can be identified.<sup>1</sup> Features of rupture-prone coronary plaques are a soft necrotic core covered by a thin fibrous cap (95% of ruptured caps are under 65  $\mu\text{m}$ ), a large plaque size, extensive remodeling, mild intraluminal stenosis, adventitial inflammation (post mortem examinations revealed that ruptured caps show macrophage infiltration), spotty calcifications and neovascularization (facilitating intra-plaque hemorrhage), many of these being detectable by imaging.<sup>9,14,18–20</sup> If vulnerable plaques could be identified before causing a major cardiac event, atherosclerosis would be a less dangerous disease. Identifying biomarkers that could predict the risk of plaque rupture with high accuracy would be a significant advance in predicting acute cardiac events in asymptomatic patients, furthermore guiding treatment of patients with this disease. The goal of this review is to focus on recent advances of noninvasive imaging of vulnerable coronary plaques.<sup>12,21</sup>

## **CONCEPT OF BIOMARKERS**

A biomarker can be defined as a characteristic that is objectively measured and evaluated, serving as an indicator of a pathogenic process, which is usually determined by laboratory measurements such as blood samples or urine, or may be a recording of a process. Key criteria are reproducibility, sensitivity, and specificity. Biomarkers can be used for disease diagnosis, therapeutic target validation and patient selection and stratification.<sup>21–24</sup> Recent studies have underlined the importance of identifying vulnerable plaques with a high risk of thromboembolic events. The main goal of noninvasive imaging should be to identify high risk lesions, specific characteristics of plaque composition and plaque activity, before any clinical event may occur.<sup>20,25,26</sup>

## **IMAGING A VULNERABLE PLAQUE**

The main indication of noninvasive imaging is to identify patients at risk based on the presence or absence of symptoms that can be related to myocardial ischemia. The diagnostic objective is to confirm or to exclude the presence of coronary plaques. Coronary imaging in asymptomatic

individuals is used to estimate the risk of future cardiac events through the identification of non-obstructive and high-risk plaques.<sup>25</sup>

The imaging modalities can be divided into two groups: invasive and noninvasive, of which the invasive methodologies include angiography, intravascular ultrasound and optical coherence tomography.<sup>21</sup> Noninvasive methodologies are ultrasound, magnetic resonance imaging (MRI), computed tomography angiography (CT), positron emission tomography (PET).<sup>27-30</sup>

### **COMPUTED TOMOGRAPHY ANGIOGRAPHY (CTA)**

Computed tomography has become one of the leading tools for diagnosing atherosclerotic disease, providing high-spatial resolution of the coronary arteries. CT-based imaging biomarkers of a vulnerable plaque include: spotty calcifications, low density atheroma, active remodeling and napkin ring sign.<sup>31</sup> Computed tomography is widely used and very reliable, as it can detect higher density calcified plaques, providing high sensitivity, on the other hand disadvantages include the inability of differentiating the different compositions of the non-calcified plaque areas, and the exposure to radiation. A study published in 2007 suggests its potential to monitor patients with atherosclerosis with statin therapy, showing that statin therapy can lead to important reduction of non-calcified plaque burden.<sup>32</sup> The coronary calcium score provides further information over cardiovascular risk, serving as an additional information to the Framingham risk score.<sup>33,34</sup> However, vulnerable plaques are predominantly non-calcified, non-stenotic, and heterogeneous in composition.<sup>33,35</sup> CT angiography with multi-detector row CT (MDCT) provides insights into the extent of atherosclerosis, allowing high-resolution imaging of the coronary artery stenoses and of the atherosclerotic plaques.<sup>30,36</sup> MDCT has become the noninvasive imaging modality of choice for significant coronary artery stenosis detection.<sup>33</sup> A study published in 2009 found a significant correlation between the presence of makers of instability detected with CT and future cardiac events, especially if three vulnerability markers are present in the same plaque (such as spotty calcification, active remodeling and low-density atheroma).<sup>3,37</sup>

### **CARDIAC MAGNETIC RESONANCE IMAGING (MRI)**

Magnetic resonance imaging is a noninvasive imaging tool, it has high resolution, provides functional charac-

terization of the plaque and soft tissues, based on proton density, perfusion, diffusion, and biochemical contrast. A full range of features that could represent plaque rupture are visible.<sup>27</sup> It can describe with high specificity and sensitivity the core with a thin fibrous cap that might be ruptured, calcifications, adventitia dimensions and intra-plaque hemorrhage and thrombosis.<sup>27,30,38</sup> MRI is showing great promise to study atherosclerosis in the coronary arteries as well as in the carotid arteries, as demonstrated in several clinical studies. Exploration of MRI applications is still evolving, especially with the improvement of different contrast agents for the assessment of molecular and cellular components of atherosclerosis.<sup>27,39</sup> With the development of special contrast agents that target some of the molecular markers of atherosclerosis and cellular components of high-risk plaques such as macrophages and endothelial adhesion molecules (for vascular inflammation), fibrin, plaque neo-vessels, MRI has become an excellent tool to monitor atherosclerotic plaque vulnerability, and overcome some of its limitations.<sup>30,40,41</sup> Cell adhesion molecules are involved in the early stages of atherosclerosis, because of their involvement in inflammation. A thrombus in the atherosclerotic plaque can be a target of molecular imaging, being a late-stage marker for atherosclerosis.<sup>42</sup> The direct imaging of thrombosis has become possible with fibrin-binding molecular contrast agents.<sup>30,43</sup> Since intra-plaque hemorrhage is considered one of the main contributors to plaque destabilization, MRI has been recently used to assess anti-angiogenic efficacy of the drugs acting on neoangiogenesis and reduce plaque vulnerability.<sup>30,44</sup>

### **POSITRON EMISSION TOMOGRAPHY (PET)**

Positron emission tomography with F-18-fluorodeoxyglucose (FDG) is a noninvasive imaging technique with high sensitivity, that helps to study human physiology and provides a measure of metabolic and functional activity based on the detection of positron emitting radiopharmaceuticals.<sup>30,45</sup> The main limitations of PET are the poor resolution, the requirement of specific radioactive tracers, and the limited availability and lengthy scan times.<sup>21,45</sup> Imaging using FDG-PET has been recently used to study the atherosclerotic mechanisms. FDG being glucose analog is thought to be an indicator for the inflammatory process, since macrophages compared to the plaque and healthy tissue have a higher glucose metabolism. Studies have shown that there is a strong association between FDG uptake and macrophage deposit. Furthermore, it positively correlates with several circulating inflammatory biomark-

ers, such as metalloproteinase which degrades the cellular matrix in the plaque.<sup>45-48</sup> In conclusion we can state that FDG uptake in vulnerable atherosclerotic lesions can have an significant clinical importance in prevention of future cardiac events.

## HYBRID TECHNIQUES

Multiple hybrid imaging techniques are available, which can target the vascular system, such as PET/CT or PET/MRI. Positron emission tomography has relatively low spatial resolution, making it necessary to use other imaging techniques such as CT or MRI. Hybrid PET/CT makes it possible to measure the functional and structural characteristics of atherosclerosis, where FDG uptake suggests atheromatous lesions with active inflammation. On the other hand, CT identifies chronic calcification, and may also detect the effect of drug treatment in correlation with inflammatory biomarkers.<sup>45,48-50</sup> Hybrid PET/MRI has great potential for cardiovascular imaging. The morphological features of carotid plaques such as lipid deposits, luminal irregularities and the inflammatory processes shown on PET demonstrate a strong association with the risk of cardiac events. Furthermore, inflammation may be associated with a higher number of vulnerable characteristics within the atheroma, emphasizing the theory that plaque inflammation and its phenotypical structure are closely linked. With the development of new imaging technologies and the introduction of combined PET and MRI scanners, it is possible to combine the positive and useful facets of each imaging modality, in order to achieve the best method for assessment of plaque morphology.<sup>50-52</sup>

## CONCLUSIONS

Atherosclerosis is a generalized disease characterized by a systemic inflammatory response, that will trigger development and progression of vascular plaques with a multifocal character. The identification of atherosclerotic lesions before any clinical events allows the introduction of appropriate strategies to prevent plaque progression and help its regression. The possibility to monitor vulnerable atheromatous lesions by using noninvasive imaging, prior to the occurrence of an acute clinical event is the main goal in plaque imaging. Investigation techniques needs to be non-invasive, reliable, inexpensive, and not harmful if multiple examinations are necessary overtime. Noninvasive imaging technologies hold great promise that well-established diagnostic technologies can be realized, may help to evalu-

ate the effectiveness of therapy and to determine high-risk patients.

## CONFLICT OF INTEREST

None declared.

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## REFERENCES

- Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of Plaque Formation and Rupture. *Circ Res*. 2014;114:1852-1866.
- Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *The Lancet*. 2017;389:197-210.
- Mitra N, Hodas R, Szabó E, Parajkó Z, Benedek T, Benedek I. Impact of Coronary Plaque Vulnerability on Acute Cardiovascular Events – Design of a CT-based 2-year Follow-up Study. *J Interdiscip Med*. 2019;4:64-71.
- Braunwald E. Epilogue: What Do Clinicians Expect From Imagers? *J Am Coll Cardiol*. 2006;47:C101-C103.
- Benedek T, Maurovich-Horváth P, Ferdinandy P, Merkely B. The Use of Biomarkers for the Early Detection of Vulnerable Atherosclerotic Plaques and Vulnerable Patients. A Review. *J Cardiovasc Emergencies*. 2016;2:106-113.
- Choi S-Y, Mintz GS. What Have We Learned About Plaque Rupture in Acute Coronary Syndromes? *Curr Cardiol Rep*. 2010;12:338-343.
- Stefanadis C, Antoniou C, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *J Am Heart Assoc*. 2017;6.
- Brown AJ, Teng Z, Evans PC, Gillard JH, Samady H, Bennett MR. Role of biomechanical forces in the natural history of coronary atherosclerosis. *Nat Rev Cardiol*. 2016;13:210-220.
- Schaar J. Terminology for high-risk and vulnerable coronary artery plaques. *Eur Heart J*. 2004;25:1077-1082.
- Davies MJ. Coronary disease: the pathophysiology of acute coronary syndromes. *Heart*. 2000;83:361-366.
- Bentzon JF, Falk E. Atherosclerosis, Vulnerable Plaques, and Acute Coronary Syndromes. In: *Genomic and Personalized Medicine*. Elsevier, 2013; p. 530-539.
- Nyulas T, Chițu M, Mester A, et al. Computed Tomography Biomarkers of Vulnerable Coronary Plaques. *Journal of Interdisciplinary Medicine*. 2016;1:263-266.
- Andreou I, Antoniadis AP, Shishido K, et al. How Do We Prevent the Vulnerable Atherosclerotic Plaque From Rupturing? Insights From In Vivo Assessments of Plaque, Vascular Remodeling, and Local Endothelial Shear Stress. *J Cardiovasc Pharmacol Ther*. 2015;20:261-275.
- Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of Vulnerable/Unstable Plaque. *Arterioscler Thromb Vasc Biol*. 2010;30:1282-1292.
- Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. *Nat Rev Immunol*. 2010;10:36-46.
- Gertz SD, Roberts WC. Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques. *Am J Cardiol*. 1990;66:1368-1372.
- Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.
- Falk E, Shah PK, Fuster V. Coronary Plaque Disruption. *Circulation*. 1995;92:657-671.
- Falk E. Pathogenesis of Atherosclerosis. *J Am Coll Cardiol*. 2006;47:C7-C12.

20. Fleg JL, Stone GW, Fayad ZA, et al. Detection of High-Risk Atherosclerotic Plaque. *JACC Cardiovasc Imaging*. 2012;5:941-955.
21. Wang X, Connolly TM. Biomarkers of Vulnerable Atheromatous Plaques. In: *Advances in Clinical Chemistry*. Vol 50. Elsevier, 2010; p. 1-22.
22. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276-1282.
23. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89-95.
24. Feuerstein GZ, Chavez J. Translational Medicine for Stroke Drug Discovery: The Pharmaceutical Industry Perspective. *Stroke*. 2009;40:S121-S125.
25. Mayeux R. Biomarkers: Potential uses and limitations. *NeuroRX*. 2004;1:182-188.
26. Wang J, Balu N, Canton G, Yuan C. Imaging biomarkers of cardiovascular disease. *J Magn Reson Imaging*. 2010;32:502-515.
27. Casscells W, Naghavi M, Willerson JT. Vulnerable Atherosclerotic Plaque: A Multifocal Disease. *Circulation*. 2003;107:2072-2075.
28. Fayad ZA, Fuster V. Clinical Imaging of the High-Risk or Vulnerable Atherosclerotic Plaque. *Circ Res*. 2001;89:305-316.
29. Crouse JR. Thematic review series: Patient-Oriented Research. Imaging atherosclerosis: state of the art. *J Lipid Res*. 2006;47:1677-1699.
30. Nahrendorf M, Jaffer FA, Kelly KA, et al. Noninvasive Vascular Cell Adhesion Molecule-1 Imaging Identifies Inflammatory Activation of Cells in Atherosclerosis. *Circulation*. 2006;114:1504-1511.
31. Jaffer FA, Libby P, Weissleder R. Optical and Multimodality Molecular Imaging: Insights Into Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2009;29:1017-1024.
32. Tarkin JM, Dweck MR, Evans NR, et al. Imaging Atherosclerosis. *Circ Res*. 2016;118:750-769.
33. Burgstahler C, Reimann A, Beck T, et al. Influence of a Lipid-Lowering Therapy on Calcified and Noncalcified Coronary Plaques Monitored by Multislice Detector Computed Tomography: Results of the New Age II Pilot Study. *Invest Radiol*. 2007;42:189-195.
34. Sarno G, Decraemer I, Vanhoenacker PK, et al. On the Inappropriateness of Noninvasive Multidetector Computed Tomography Coronary Angiography to Trigger Coronary Revascularization. *JACC Cardiovasc Interv*. 2009;2:550-557.
35. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary Calcification, Coronary Disease Risk Factors, C-Reactive Protein, and Atherosclerotic Cardiovascular Disease Events. *J Am Coll Cardiol*. 2005;46:158-165.
36. Tardif J-C, Lesage F, Harel F, Romeo P, Pressacco J. Imaging Biomarkers in Atherosclerosis Trials. *Circ Cardiovasc Imaging*. 2011;4:319-333.
37. Adamson PD, Newby DE. Non-invasive imaging of the coronary arteries. *Eur Heart J*. 2019;40:2444-2454.
38. Schroeder S, Kopp AF, Baumbach A, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. This study was performed without additional financial support. *J Am Coll Cardiol*. 2001;37:1430-1435.
39. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319-326.
40. Lindsay AC, Choudhury RP. Form to function: current and future roles for atherosclerosis imaging in drug development. *Nat Rev Drug Discov*. 2008;7:517-529.
41. Amirbekian V, Lipinski MJ, Briley-Saebo KC, et al. Detecting and assessing macrophages in vivo to evaluate atherosclerosis noninvasively using molecular MRI. *Proc Natl Acad Sci*. 2007;104:961-966.
42. McAtteer MA, Schneider JE, Ali ZA, et al. Magnetic Resonance Imaging of Endothelial Adhesion Molecules in Mouse Atherosclerosis Using Dual-Targeted Microparticles of Iron Oxide. *Arterioscler Thromb Vasc Biol*. 2008;28:77-83.
43. Mitsumori LM, Hatsukami TS, Ferguson MS, Kerwin WS, Cai J, Yuan C. In vivo accuracy of multisequence MR imaging for identifying unstable fibrous caps in advanced human carotid plaques. *J Magn Reson Imaging*. 2003;17:410-420.
44. Botnar RM, Buecker A, Wiethoff AJ, et al. In Vivo Magnetic Resonance Imaging of Coronary Thrombosis Using a Fibrin-Binding Molecular Magnetic Resonance Contrast Agent. *Circulation*. 2004;110:1463-1466.
45. Winter PM, Neubauer AM, Caruthers SD, et al. Endothelial  $\alpha v \beta 3$  Integrin-Targeted Fumagillin Nanoparticles Inhibit Angiogenesis in Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2006;26:2103-2109.
46. Motoyama S, Sarai M, Harigaya H, et al. Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome. *J Am Coll Cardiol*. 2009;54:49-57.
47. Rudd JHF, Warburton EA, Fryer TD, et al. Imaging Atherosclerotic Plaque Inflammation With [ $^{18}$ F]-Fluorodeoxyglucose Positron Emission Tomography. *Circulation*. 2002;105:2708-2711.
48. Tawakol A, Migrino R, Hoffmann U, et al. Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. *J Nucl Cardiol*. 2005;12:294-301.
49. Wu Y-W, Kao H-L, Huang C-L, et al. The effects of 3-month atorvastatin therapy on arterial inflammation, calcification, abdominal adipose tissue and circulating biomarkers. *Eur J Nucl Med Mol Imaging*. 2012;39:399-407.
50. Figueroa AL, Subramanian SS, Cury RC, et al. Distribution of Inflammation Within Carotid Atherosclerotic Plaques With High-Risk Morphological Features: A Comparison Between Positron Emission Tomography Activity, Plaque Morphology, and Histopathology. *Circ Cardiovasc Imaging*. 2012;5:69-77.
51. Ishii H, Nishio M, Takahashi H, et al. Comparison of Atorvastatin 5 and 20 mg/d for Reducing F-18 Fluorodeoxyglucose Uptake in Atherosclerotic Plaques on Positron Emission Tomography/Computed Tomography: A Randomized, Investigator-Blinded, Open-Label, 6-Month Study in Japanese Adults Scheduled for Percutaneous Coronary Intervention. *Clin Ther*. 2010;32(14):2337-2347.
52. Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. *Nature*. 2008;451:953-957.