Atherosclerosis 229 (2013) 34–37

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

Do vulnerable and ruptured plaques hide in heavily calcified arteries?

Fumiyuki Otsuka [a], Aloke V. Finn [b,1], Renu Virmani [a,*,2]

[a] CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA
[b] Department of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 21 December 2012
Accepted 28 December 2012
Available online 9 January 2013

Keywords:
Coronary calcification
Plaque vulnerability
Pathology

Coronary calcification is an inevitable component of advanced atherosclerosis. Clinical studies have demonstrated that the presence of coronary artery calcification (CAC) in asymptomatic individuals detected by computed tomography (CT) is a predictor of future cardiac events over and above Framingham risk score [1,2]. A recent large population-based study with 5-year follow-up period showed that adding CAC score (≥400 Agatston score) to intermediate Framingham risk score and Adult Treatment Panel scores of 10–20% and 6%–20% results in reclassification to the high-risk category for coronary death and nonfatal myocardial infarction [3]. In patients presenting with acute coronary syndromes (ACS) versus those with stable angina, coronary calcification is frequently identified by multislice CT (MSCT) at culprit site, where the majority of the ACS plaques showed spotty calcification, low plaque density, and positive remodeling whereas stable plaques had large calcification and infrequent remodeling [4].

Pathologists have recognized the presence of calcification in atherosclerotic coronary arteries for over a century. There are two forms of calcification, one involving the media (Mönckeberg's medial calcification) and the other within the intima. The intimal calcification of the atherosclerotic plaques begins with the death of smooth muscle cells and macrophages and eventually involves the necrotic core and the collagen-rich extracellular matrix. There is great controversy regarding the mechanisms of intimal calcification with parallels being drawn between arterial calcification and osteogenesis. The theory that osteogenesis is the main mechanism of arterial calcification is mostly based on the fact that bone formation is observed in areas of arterial atherocalcification; however, this phenomenon is rare and only occurs in the arteries that are already heavily calcified. Also, bone related proteins have been reported to be present, but these are only observational studies and/or from in vitro cell culture studies that are extrapolational [5]. Coronary calcification is known to be influenced by systemic factors such as age, gender, renal function, diabetes, vitamin D levels with other aspects of bone metabolism, and genetic variations [6–9].

At autopsy, coronary calcification has been shown to correlate with plaque burden. There is, however, only a weak correlation between calcification and severity of luminal narrowing [10]. The extent of calcification is also dependent on plaque morphology; the least calcification is seen in plaque erosion and the maximum in healed plaque ruptures [6]. In sudden coronary death victims, most acute plaque ruptures show some calcification; however, approximately 70% have only speckled calcification which may not be easily detected on fluoroscopy or MSCT or intravascular ultrasound (IVUS) [11]. Similarly, over 50% of thin-cap fibroatheromas (TCFAs) or vulnerable plaques show either no or speckled calcification [11]. In line with previous observations from clinical imaging studies in patients with ACS [4], autopsy studies have identified less calcification in ruptured or vulnerable plaques as compared to stable plaques in sudden coronary death victims (Fig. 1). Interestingly, the extent of calcification in ruptured or vulnerable plaques does not

DOI of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2013.03.010.
* Corresponding author. Tel.: +1 301 208 3570; fax: +1 301 208 3745.
E-mail address: rvirmani@cvpath.org (R. Virmani).
[1] Dr. Finn is supported by the NIH grant HL096970-01A1, the American Heart Association, the Woodruff Sciences Health Center and Carlyle Fraser Heart Center both at Emory University, sponsored research agreement with Medtronic and Boston Scientific, and is a consultant for Medtronic.
[2] Dr. Virmani is a consultant for Abbott Vascular, 480 Biomedical, Atrium Medical, Merck, Lutonix, Medtronic AVE, and W.L. Gore.

http://dx.doi.org/10.1016/j.atherosclerosis.2012.12.032

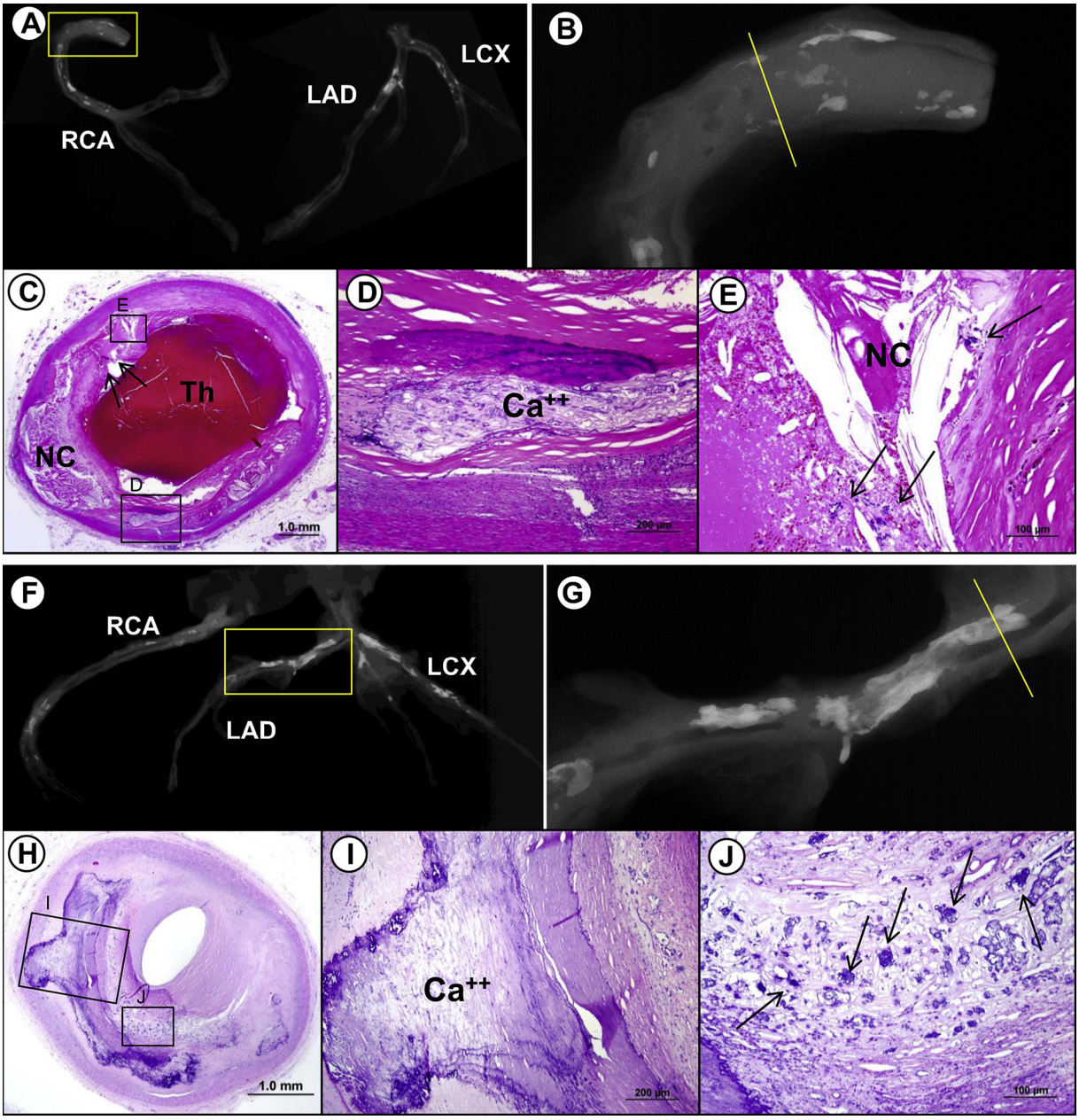

Fig. 1. Calcification in ruptured and stable coronary plaques. (A–E) Radiographs and histologic sections from a 61-year-old man who died suddenly due to acute coronary thrombosis caused by plaque rupture. (A) The radiograph of the major coronary arteries removed at autopsy shows mild focal calcification of the right (RCA), the left circumflex (LCX), and the left anterior descending (LAD) coronary arteries. (B) A high-power magnification of the radiograph from the boxed area in (A) shows speckled and fragmented calcification in proximal RCA. (C) A low-power image of acute plaque rupture (arrow) with occlusive luminal thrombus (Th) from the proximal RCA corresponding to the yellow line in (B). Note presence of underlying necrotic core (NC). (D and E) High-power images showing fragmented (Ca^{++}) (D) and speckled calcification (arrows) presumably resulting from apoptotic macrophages within the necrotic core (E). (F to J) Radiographs and histologic sections from a 54-year-old man who died suddenly from severe coronary artery disease. (F) The radiograph shows severe calcification in LAD and LCX and mild calcification in RCA. (G) A high-power radiographic image of the boxed area in (F) shows diffuse calcification in proximal LAD. (H) A low-power image of a stable plaque from proximal LAD corresponding to yellow line in (G) shows presence of severe luminal narrowing and extensive calcification (fibrocalcific plaque). (I and J) High-power images showing sheet-like calcification (I) and speckled calcification (J, arrows).

change substantially across the decades, whereas calcification area in stable plaques increases steadily with advancing age (Fig. 2).

In this issue of *Atherosclerosis*, Mauriello et al. [12] report the results of a morphologic and morphometric study evaluating serial histologic sections of coronary arteries obtained from patients who died from acute myocardial infarction (AMI) and comparing these to patients dying from non-cardiac causes. They found that patients with AMI had greater atherosclerotic burden with more extensive calcification as compared to the age-matched controls, whereas the degree of calcification in unstable (vulnerable and ruptured) plaques was significantly less than that in stable plaques. The extent of calcification correlated inversely with fibrous cap inflammation, and calcification was not identified as an independent determinant of unstable plaques in multivariate analysis [12]. While these findings complement aforementioned previous observations, the investigators failed to assess the additive benefit of CAC over traditional risk factors for the prediction of AMI or plaque rupture. Previous pathologic studies have reported an