JACC: CARDIOVASCULAR IMAGING
VOL. 4, NO. 6, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.01.019

EDITORIAL COMMENT

Are Our Tools for the Identification of TCFA Ready and Do We Know Them?*

Renu Virmani, MD
Gaithersburg, Maryland

The current understanding of the cause of acute coronary syndromes is that most result from plaque rupture of a vulnerable plaque. The word "vulnerable" plaque was coined by Muller et al. (1) to define lesions that underlie luminal thrombosis. The definition was further clarified by Libby (2) to include fibrous cap infiltration by macrophages and T-lymphocytes at shoulder regions of the plaque; the latter release interferon-gamma, which suppress collagen deposition by smooth muscle cells, whereas

See pages 638 and 647

the former secrete matrix metalloproteinases degrading collage fibers with subsequent plaque rupture. In 1997 Burke et al. (3) defined vulnerable plaques (thin-cap fibroatheromas [TCFA]) as lesions with a fibrous cap <65 μm with macrophage infiltration (>25 cells/high-magnification [0.3 mm diameter] field) and an underlying necrotic core. Subsequently, we showed that TCFA had a significantly smaller necrotic core and less macrophage infiltration of the fibrous cap than ruptured plaques (4) (Fig. 1). Since the 1980s, it has been appreciated that plaque progression is associated with positive remodeling (5) and that the highest remodeling index is seen in plaque ruptures (6). Plaque ruptures and TCFA tend to occur at proximal locations of the coronary arteries (4). Therefore, accurate identification of these vulnerable lesions has become the "holy grail" of interventional cardiology with the idea that, if we could identify these sites before rupture, we could then treat them by interventional means or even medically to prevent clinical events, reducing both morbidity and mortality.

Many invasive and noninvasive imaging modalities have been introduced to identify the TCFA. Intravascular ultrasound (IVUS) (resolution approximately 200 μm) for plaque area and volume measurement has been around for a long time; however, although it does characterize calcified areas, it has limited capability to identify "necrotic core" and "lipid pools" (7). Recently, 2 new techniques that use ultrasound-based radiofrequency signals (virtual histology [VH]) and integrated backscatter (IB) values have characterized the plaque areas that contain "necrotic core" or "lipid pool"; dense fibrosis or fibrosis; fibrofatty or fibrosis; and dense calcification or calcification, respectively (8,9). Some investigators (10) claim that the latter provides higher accuracy than the former. Another technique, optical coherence tomography (OCT), with a resolution of 15 to 20 μm, has the ability to measure coronary microstructure including fibrous cap thickness <65 μm and macrophage infiltration; however, it has limited depth of penetration (1.0 to 1.5 cm) (11,12). Because the presence of necrotic core is an important component of TCFA, near-infrared spectroscopy—which has otherwise been used to determine chemical composition of substances—seems highly suitable to identify cholesterol ester and free cholesterol and is available in an intravascular catheter system (13).

Having been involved at some stage of the introduction of these catheter-based new technologies, I believe it is important to critically examine whether any or all of them are capable of identifying TCFA, a lesion that we all believe as a critical predecessor of plaque rupture. Let us first discuss VH-IVUS, which was introduced in 2002. I believe there is oversimplification of manner by which the

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From CVPath Institute, Inc., Gaithersburg, Maryland. Dr. Virmani has relationships with Abbott Vascular, Arsenal Medical, Atrium Medical Corp., Biosense International, GlaxoSmithKline, Lutonix, Medtronic Ave, and W.L. Gore.

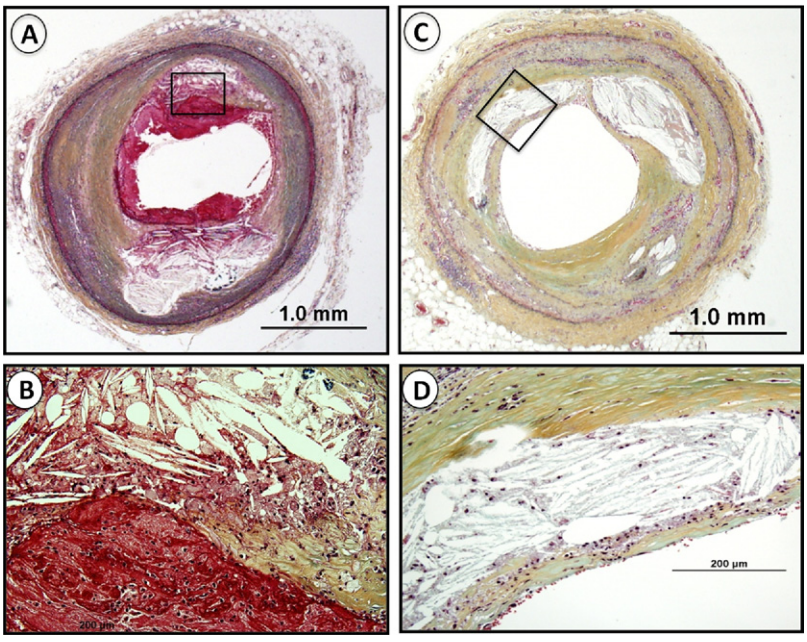

Figure 1. Photomicrographs of Plaque Rupture and Thin-Cap Fibroatheroma

Plaque rupture (**A and B**) and thin-cap fibroatheroma (**C and D**). **Boxed areas** in **A** and **C** show the thin fibrous cap, which is infiltrated by macrophages; **B** is rupture site, and **D** shows intact fibrous cap.

TCFA is recognized with this modality. Because the resolution is 150 to 200 μm, it is incapable of identifying the fibrous cap thickness component of TCFA (i.e., $<$65 μm). How accurate is the technology for the identification of "necrotic core?" I believe its accuracy in separating "lipid pool" from "necrotic core" is questionable, as there is a fair amount of overlap. This separation is critical to calling a lesion "fibroatheroma" or TCFA, because necrotic core (not lipid pool) is a critical feature. Another IVUS-based technology, IB-IVUS, similarly lacks resolution, because it cannot identify "thin cap" of TCFA, and it too does not separate "lipid pool" from "necrotic core." It also likely "over-calls" areas of lipid-rich lesion and, therefore, the percent lipid pool area is significantly larger than what is actually present in the lesions.

By contrast, there is no question that OCT is far superior (10 to 20 μm), from the point of resolution and, therefore, can identify thin caps of TCFA. However, it is not always easy to separate "calcified area" from "necrotic core," because it is dependent on attenuation of the signals (i.e., abrupt for calcium vs. gradual for "necrotic core"); in experienced hands I believe this should not be such a problem. However, OCT is unable to give us vessel dimensions, plaque area, or "necrotic core" area, because of limitation of depth penetration of the vessel wall. These parameters (i.e., vessel remodeling as well as plaque area), can be assessed by IVUS, VH, and IB-IVUS though as indicated, both likely overestimate lipid core area and may have limited capability for assessing vulnerability index.

Near-infrared spectroscopy is not image-based but assesses presence of cholesterol monohydrate and cholesterol ester, which are high in necrotic cores, as reported by Mann and Davies (14) in disrupted plaques. Near-infrared spectroscopy gives a "chemogram," and in validation studies "fibroatheromas" were defined as representing lesions with a lipid core of $>60^{\circ}$ in circumference and $>$200 μm. It has the limitation that it does not measure fibrous cap; therefore, it too cannot separate fibroatheromas from TCFA. However, its ability to recognize presence of free cholesterol is far superior to IVUS- or OCT-based techniques. Therefore, none of the technologies available individually gives us great confidence of their ability to detect presence of TCFA with the accuracy that is required to make inroads into the prevention of acute coronary syndrome.

Let us assume that a combination of devices detect presence of TCFA with certain accuracy, and if so, we need to understand as to what we are likely to gain. It has long been appreciated that plaque progression beyond 50% cross-sectional area nar-

JACC: CARDIOVASCULAR IMAGING, VOL. 4, NO. 6, 2011
JUNE 2011:656–8

rowing in a vast majority of cases occurs through repeated rupture, which occur silently (15). Mann and Davies (14) in the late 1990s showed that healed plaque ruptures were most frequently seen in lesions with diameter stenosis >50% (73%). We showed that the incidence of healed rupture was highest in stable plaques with healed myocardial infarction, followed by acute ruptures, and least in stable plaque without a healed myocardial infarction (80%, 75%, 53%, respectively) (15). Healed and acute ruptures are most frequently located at proximal, followed by middle, and least frequently located in distal coronary arteries. Also, the luminal narrowing increased with increasing number of healed plaque ruptures. Only 11% of cases with acute rupture had not had a previous rupture site (i.e., virgin ruptures) (15). Therefore, it is clear that not all plaque ruptures will lead to clinical symptomatology.

Therefore, for further understanding of plaque characteristics, we need to identify lesions that are vulnerable (i.e., TCFA) and follow these patients for symptom development and also re-interrogate the lesion at a specified time (1 to 2 years) to determine what number would have ruptured either silently or producing symptoms. The most important morphology for the identification of TCFA is the presence of a large necrotic core, thin fibrous cap, and positive remodeling; and if we can have everything, then I would certainly add macrophage infiltration of the fibrous cap and angiogenesis. Until we are able to identify TCFA with a high sensitivity and specificity, we will fail in our endeavor to understand how plaque evolution leads to symptom development and plaque progression, because both are essential if we are to treat patients who have vulnerable lesions along with risk factors (14).

Reprint requests and correspondence: Dr. Renu Virmani, CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, Maryland 20878. *E-mail: virmani@cvpath.org.*

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Key Words: integrated backscatter intravascular ultrasound ■ near-infrared spectroscopy ■ optical coherence tomography ■ thin-cap fibroatheroma ■ virtual histology.