Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 10, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.04.085

EDITORIAL COMMENT

From Postmortem Characterization to the In Vivo Detection of Thin-Capped Fibroatheromas: The Missing Link Toward Percutaneous Treatment

What If Diogenes Would Have Found What He Was Looking For?*

Patrick W. Serruys, MD, PHD, FACC,
Hector M. Garcia-Garcia, MD, MSC, FACC,
Evelyn Regar, MD, PHD

Rotterdam, the Netherlands

In this issue of the *Journal*, Kubo et al. (1) and Cheruvu et al. (2) provide essential anatomical information about plaques that cause acute coronary thrombotic occlusion and their postulated precursors, thin-capped fibroatheromas (TCFAs). Histopathological assessment (Cheruvu et al. [2]) of the epicardial vascular tree revealed that the incidence of TCFAs and ruptured plaques is low and their spatial distribution is focal. An in vivo investigation of patients with acute myocardial infarction (Kubo et al. [1]) confirmed that, indeed, ruptured TCFA is the predominant morphologic substrate. Linking these observations together can cast light on possible options for treatment of such coronary lesions.

See pages 933 and 940

From Postmortem Observations to the In Vivo "Hot Plaque" Characterization

The current paradigm postulates a particular morphology for so-called vulnerable plaques, including a thin fibrous cap overlying a necrotic-rich core. However, it is difficult to translate postmortem findings into a prospective, prognostically relevant concept for patients.

When is a fibrous cap considered thin? Pioneering pathology studies applied various criteria regarding study population, region of interest, and cap definition. Mann and Davies (3) reported on 160 coronary plaques obtained from 31 subjects who died of sudden cardiac death. Mean cap thickness was 250 μm (range 20 to 1,140 μm) in types IV and V plaques. Burke et al. (4) sectioned coronaries at 3-mm intervals. Only cross sections with more than 50% lumen narrowing were analyzed. In ruptured plaques, fibrous cap thickness was 23 $\pm$ 19 μm, and in 95% of these plaques cap thickness was $<$65 μm. This value of cap thickness of *ruptured plaques* has been used—maybe inappropriately—for the definition of *nonruptured* TCFA (5), despite the fact that TCFAs have less necrotic core, less cholesterol clefts, and less macrophage infiltration compared with ruptured plaque.

The present reports use the $<$65-μm criterion to define TCFA. However, there is no consensus among clinicians and pathologists regarding the critical threshold for cap thickness that would reliably predict imminent plaque rupture. The criticism of clinicians stems from the fact that application of absolute histomorphometric values can be misleading due to anisotropic tissue shrinkage and to the lack of longitudinal data. In addition, the absence of a technique able to provide an accurate cap assessment in vivo has resulted in a lack of knowledge on the natural history of such plaques.

Optical coherence tomography (OCT), the optical analogue to pulse-echo ultrasound imaging, can directly visualize a thin fibrous cap. Currently, intracoronary OCT systems work with a resolution of 10 to 15 μm. Cilingiroglu et al. (6) demonstrated that OCT is able to accurately visualize thin fibrous caps in vivo (7). Optical coherence tomography can evaluate the macrophage content (7–9) and the collagen composition of a fibrous cap (7). In the current issue, Kubo et al. (1) evaluated the ability of intracoronary OCT to assess culprit lesions during primary percutaneous coronary intervention in patients with acute myocardial infarction. Optical coherence tomography was superior in detecting plaque rupture and erosion as compared with intravascular ultrasound (IVUS) and angioscopy. The study is remarkable in several respects. Obviously, it demonstrates the feasibility of a complex imaging protocol including IVUS, angioscopy, and OCT in the acute setting. Secondly, it confirms the pathology-driven hypothesis of the prominent role of TCFA rupture in acute coronary thrombotic occlusion. Third, it allows for the first time in vivo estimation of critical cap thickness in patients. The thickness of the remnants of the fibrous cap after symptomatic rupture measured in vivo was 49 $\pm$ 21 μm. These observations represent a very encouraging step toward a prospective, in-vivo evaluation of "hot" plaques at high risk for acute coronary events. However, the results should be interpreted with caution. The incidence of plaque rupture cannot be generalized, as there was considerable selection bias in the

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

From the Thoraxcenter, Rotterdam, the Netherlands.

study cohort. Optical coherence tomography differentiation of necrotic-rich core from calcified plaque by visual assessment of the gray scale image can be difficult (10). Therefore, it would important to know the actual intra- and interobserver variability of Kubo et al. (1) to assess the accurateness of their results.

When Distribution and Frequency Matters

As atherosclerosis is a systemic disease, plaque rupture is considered a ubiquitous process that may be clinically silent or symptomatic in different regions of the vascular system. In patients with acute coronary syndrome (ACS), Rioufol et al. (11) reported at least 1 plaque rupture remote from the culprit lesion in 80% and remote from the culprit artery in 71% of their patients. A meta-analysis described that more than 20% of ACS patients have more than 1 ruptured plaque (12). Likewise, a high prevalence of rupture-prone lesions throughout the coronary tree has been reported by angiography (13), angioscopy (14), and palpography (15).

The report of Cheruvu et al. (2) is at variance with previous reported data. First, the prevalence of TCFA and ruptured plaques is *low* (0.46 ± 0.95 and 0.38 ± 0.70 per heart, respectively), *focal*, and located in the *proximal segments* of the coronaries. In earlier studies, up to 3 TCFA were found per heart (16). Explanations for this might be demographic differences in studied population and in methods, namely *longitudinal* instead of cross-sectional cutting of the coronaries. Second, necrotic core size was relatively *small* for both, TCFA (1.6 ± 1.8 mm^2; length 2.7 ± 2.0 mm) and ruptured plaques (2.2 ± 1.9 mm^2; length 1.9 ± 3.6 mm). In previous studies, the size of necrotic core in TCFAs was 1.7 ± 1.1 mm^2 with a length of 8 mm (range 2 to 17 mm), and in ruptured plaques 3.8 ± 5.5 mm^2, with a length of 9 mm (range 2.5 to 22 mm) (5). The difference in length is striking. Therefore, we may wonder whether the intrinsic risk varies among the type of lesions that are labeled by the same morphologic term "TCFA."

The Cheruvu et al. (2) findings have potentially important clinical implications, since maybe only TCFA that are proximally located, with large necrotic core and outward remodeling, should be considered for local treatment. Unfortunately, remodeling index is not reported, likely due to the methodology (longitudinal cut in 4 quadrants).

To date, there is no single marker that can accurately identify the risk of rupture for an individual plaque. But it has been suggested that assessment of several plaque characteristics (morphologic, biochemical, and mechanical) may improve the ability to correctly diagnose vulnerable plaques. Radiofrequency IVUS data analysis (e.g., virtual histology, palpography) has emerged as a tool to potentially detect TCFAs in vivo. In a recent study, patients with ACS underwent IVUS-VH analysis of all 3 epicardial coronaries. On average, there were 2 IVUS-derived TCFA per patient with half of them showing outward remodeling (17). Interestingly, the size of the necrotic core (1.2 ± 0.8 mm^2) is in line with the Cheruvu et al. (2) histopathological data. Another interesting approach is the combination of VH and palpography. Both datasets can be simultaneously acquired during one single IVUS pullback, allowing for the assessment of both morphologic and biomechanical properties of a particular plaque. Assessing several characteristics of a given plaque could potentially enhance invasive risk stratification by identifying very high-risk plaques, thereby lowering the number of vulnerable plaques that deserve to be followed over time and ultimately treated.

What If Diogenes Would Have Found What He Was Looking For?

The cynic Greek philosopher Diogenes walked through Athens in broad daylight carrying a lighted lamp, looking for an honest man. Needless to say, he never found one.

What if we ever *became* able *to identify* in vivo the uncommon TCFAs on the verge of imminent rupture? Vessel wall *re*inforcement should be considered mandatory. Ideally, lesion coverage and cap *re*inforcement by a dedicated shield with thin and dense struts (permanent or preferably absorbable) strong enough to progressively change the geometry of the lumen by self-expansion without rupturing the cap would be appealing. Computational finite element and fluid dynamics taught us that geometrical changes in lumen shape can affect local mechanics unfavorably or favorably, either leading to plaque rupture or to *re*inforcement of the thin fibrous cap (18,19). Finally, having acutely constrained the necrotic core, it should subsequently be reduced by a pharmacologic agent or mechanically. Furthermore, *re*generation of the endothelium and *re*covery of its functionality, possibly by passive or active endothelial cell attraction, would heal the endothelial lining, while drugs specifically targeting the necrotic core could be released abluminally. Such newly designed absorbable stents are currently contemplated as future focal treatment for vulnerable plaque.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Thoraxcenter, Ba583, Dr. Molewaterplein 40, 3015-GD Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol 2007;50:933–9.
2. Cheruvu PK, Finn AV, Gardner C, et al. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. J Am Coll Cardiol 2007;50:940–9.
3. Mann JM, Davies MJ. Vulnerable plaque. Relation of characteristics to degree of stenosis in human coronary arteries. Circulation 1996;94:928–31.
4. Burke AP, Farb A, Malcom GT, Liang Y-H, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276–82.
5. Virmani R, Burke AP, Kolodgie FD, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. J Interv Cardiol 2002;15:439–46.

JACC Vol. 50, No. 10, 2007
September 4, 2007:950–2

6. Cilingiroglu M, Oh JH, Sugunan B, et al. Detection of vulnerable plaque in a murine model of atherosclerosis with optical coherence tomography. Cathet Cardiovasc Intervent 2006;67:915–23.
7. Regar E, van Leeuwen AMGJ, Serruys PW. Optical Coherence Tomography in Cardiovascular Research. London: Informa Healthcare, 2007.
8. Tearney GJ, Yabushita H, Houser SL, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation 2003;107:113–9.
9. MacNeill BD, Jang IK, Bouma BE, et al. Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. J Am Coll Cardiol 2004;44:972–9.
10. Manfrini O, Mont E, Leone O, et al. Sources of error and interpretation of plaque morphology by optical coherence tomography. Am J Cardiol 2006;98:156–9.
11. Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. Circulation 2002;106:804–8.
12. Libby P. Act local, act global: inflammation and the multiplicity of "vulnerable" coronary plaques. J Am Coll Cardiol 2005;45:1600–2.
13. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000;343:915–22.
14. Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. J Am Coll Cardiol 2001;37:1284–8.
15. Schaar JA, Regar E, Mastik F, et al. Incidence of high-strain patterns in human coronary arteries: assessment with three-dimensional intravascular palpography and correlation with clinical presentation. Circulation 2004;109:2716–9.
16. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385–91.
17. Garcia-Garcia HM, Goedhart D, Schuurbiers JC, et al. Virtual histology and remodeling index allow in vivo identification of allegedly high risk coronary plaques in patients with acute coronary syndromes: a three vessel intravascular ultrasound radiofrequency data analysis. Eurointervention 2006;2:338–44.
18. Slager CJ, Wentzel JJ, Gijsen FJ, et al. The role of shear stress in the generation of rupture-prone vulnerable plaques. Nat Clin Pract Cardiovasc Med 2005;2:401–7.
19. Slager CJ, Wentzel JJ, Gijsen FJ, et al. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. Nat Clin Pract Cardiovasc Med 2005;2:456–64.