EDITORIAL COMMENT

Intravascular Ultrasound Tissue Characterization

Messages From the Heart*

Sanjay Kaul, MD,†‡§ George A. Diamond, MD‡§

Los Angeles, California

Why are there so many
Songs about rainbows
And what's on the other side
Rainbows are visions
They're only illusions
And rainbows have nothing to hide

—Kermit the Frog
The Rainbow Connection (1)

Cardiac biomarkers of necrosis have been described as providing clinicians with important "messages" from the heart (2). They play an integral role in the clinical diagnosis of myocardial infarction (MI). In addition to providing diagnostic information, cardiac biomarkers also offer clinicians a valuable tool for prognostication and therapeutic decision making. The European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation task force recently codified myocardial infarction into 5 types

(3). Of particular interest, especially to the interventional cardiologist, is the type 4a, MI associated with percutaneous coronary intervention (PCI). The universal definition of MI arbitrarily defines a post-PCI MI, among patients with normal pre-procedural values, as an increase in biomarker value that is >3× the upper limit of normal (99th percentile). Cardiac troponins are the preferred biomarker of choice in defining post-PCI MI (3).

A large number of studies have shown that mild-to-moderate elevations of cardiac biomarkers are detected in 10% to 43% of cases after PCI (2–4). Elevations of cardiac troponins occur more frequently than elevations of creatine kinase (CK)-MB after elective PCI. Although post-procedural cardiac troponin level elevation is associated with abnormal tissue-level perfusion (5) and irreversible myocardial injury (6), the clinical and prognostic impact of post-procedural cardiac biomarker release is not unambiguously established. Studies have yielded inconsistent results, with some reporting that an elevated troponin level is, and others that it is not, an independent predictor of survival (2–4). Interpretations have ranged from a direct cause-and-effect association between any level of biomarker elevation and subsequent mortality to the biomarker elevations representing a marker of high risk such as disease severity, plaque characteristic, or inflammatory status. More recently, studies have indicated that pre-procedural rather than post-procedural cardiac troponin level is a powerful independent predictor of prognosis (4).

An important implication of the argument that there is a relationship between the cardiac biomarker released and long-term risk of adverse cardiac outcomes is that prevention of periprocedural MI, either through a priori identification of the plaques that are associated with these events and/or by the use of drugs and devices that reduce periprocedural MI, would be desirable. In this issue of *iJACC*, Hong et al. (7) study the relationship of pre-PCI measures of plaque composition and post-PCI cardiac troponin I (cTnI) elevation in 80 selected patients undergoing nonurgent PCI at a single center over a 1-year period from 2005 to 2006. The plaque composition was assessed by virtual histology (VH)-intravascular ultrasound (IVUS) (Volcano Therapeutics, Inc., Rancho Cor-

---

dova, California), in which spectral analysis of radiofrequency ultrasound backscatter signals from the IVUS images are displayed in a rainbow of colors to define fibrous (green), fibro-fatty (yellow-green), dense calcific (white), and necrotic core (red) areas within the plaque. The principal finding was that the plaque necrotic area was an independent predictor of post-PCI TnI elevation. The investigators conclude that "VH-IVUS may play an important role detecting which lesions are high risks for myocardial necrosis after PCI."

Identification of plaque at high risk for distal embolization or myonecrosis remains a challenge during coronary interventions. Tissue characterization of plaque components by VH-IVUS might provide useful information in this setting, thereby offering an opportunity for validation of the clinical utility of this technology. Accordingly, several studies have focused on the identification of markers of distal embolization in patients with acute MI, unstable angina, or stable angina using the VH-IVUS technology (8–11). In patients with ST-segment elevation myocardial infarction undergoing primary stenting, a positive correlation was found between plaque necrotic core volume and ST-segment re-elevation (surrogate marker for distal embolization) in the study by Kawaguchi et al. (8). However, in another study by Nakamura et al. (9), the appearance of no-reflow was not correlated to the volume of necrotic core. Kawamoto et al. (10) investigated the relationship between VH findings and high-intensity transient signals by intracoronary Doppler (surrogate for small particle embolization) and observed that only necrotic core area emerged as an independent predictor of Doppler-detected distal embolization. Using integrated backscatter-IVUS technology, Uetani et al. (11) recently showed in relatively stable patients undergoing elective coronary stenting that myonecrosis assessed by CK-MB and troponin-T in single blood samples at 18 h was directly related to the relative lipid volume and inversely related to the relative fibrous volume. These observations are consistent with those reported in the present study.

The authors have investigated an important issue that is very relevant to daily interventional cardiology practice. In contrast to previous studies that relied on surrogate markers, they directly assessed myonecrosis to evaluate implications of plaque components on periprocedural complications. The authors are appropriately cautious in the interpretation of these observations as being hypothesis-generating and calling for their verification in ade-

quately powered prospective evaluations. Nonetheless, to place their observations into context, some methodological issues with VH-IVUS technology merit consideration.

The development of VH-IVUS offers us the possibility of identifying vulnerable or rupture-prone atherosclerotic plaques, the pathological substrate underlying up to 75% of episodes of acute coronary syndromes and the most common cause of sudden death, by providing detailed assessment of plaque composition in vivo. It has the potential to provide new insights into the pathophysiology of coronary artery disease and may allow for better treatment stratification. However, before endorsing VH-IVUS, improvements in the existing technology that can better distinguish plaque morphology are needed. For example, the spatial resolution of VH-IVUS (100 to 200 μm) is far below that needed to detect vulnerable plaque characterized by a necrotic core with an overlying fibrous cap of <65 μm thickness, the so-called thin-cap fibroatheroma. These improvements in technology might also overcome its current limitations in distinguishing necrotic core from calcification and in border detection, thereby avoiding spurious conclusions about culprit plaque composition. Currently, optical coherence tomography yields a higher spatial resolution (10 to 20 μm), and offers the potential to provide more accurate information on coronary plaques. However, this technology is limited by its inability to image through blood and lack of penetration of deeper regions of plaque, thus rendering it unwieldy and curtailing its widespread use as a diagnostic tool. Although VH-IVUS technology has been validated in human coronary arteries in ex vivo and in vivo studies with reasonably good predictive accuracies, the virtual histological definition of vulnerable plaque awaits validation against histopathological features. Furthermore, studies comparing VH-IVUS with noninvasive imaging tools such as multislice computed tomography and cardiac magnetic resonance are required to evaluate the optimal performance of these technologies in plaque characterization.

In addition to the limitations stated by the authors, other limitations of the current study need to be acknowledged.

First, a previous study reported a strong positive correlation between necrotic core and dense calcium volumes (8). Thus, it is unclear whether calcium is implicated in distal embolization and myonecrosis.

Second, tissue characterization by VH-IVUS is currently unable to distinguish intralesion throm-

bus, a key contributor to distal embolization, from lipid-rich components of the atherosclerotic plaque, thereby confounding plaque assessment.

Third, the bulk of the friable material near to the lumen may be disrupted with the simple passage of the IVUS catheter (Dotter effect). Therefore, tissue characterization will only be able to analyze the residual material left on the vessel wall. Given this, it is extremely difficult to distinguish the effects of the interventional procedure from the IVUS procedure that preceded it on post-procedural biomarker values.

Fourth, although statistically significant, the correlation between the necrotic core fraction (r = 0.31, p = 0.005) and fibro-fatty fraction (r = −0.27, p = 0.015) at the minimum lumen site with post-PCI cTnI was rather modest.

Fifth, it is not clear which patient-related, lesion-related, and procedure-related variables were entered into the univariable and multivariable models. In addition, multiple regression models are unable to account for unobserved covariates that may be confounded with troponin. Furthermore, even though the area under the receiver-operator characteristic curve for absolute necrotic core area at the minimum lumen site predicting post-PCI MI was reported to be 0.914, indicating a high discriminant value, the incremental value of necrotic core area over patient-related, lesion-related, and procedure-related variables in predicting post-PCI biomarker elevation was not provided. Thus, it is unclear what additional relevant information, independent of these variables, can be gained from routine tissue characterization by VH-IVUS pre-PCI.

Sixth, although the authors used the universal MI definition criterion of >3× the upper limit of normal (99th percentile) as PCI-related MI (type 4a), it is important to emphasize the arbitrary nature of this criterion (3). Nonetheless, using this arbitrary cutoff, post-PCI MI occurred frequently (nearly 50%). Although the magnitude of the increase in cTnI is not clear, the frequency of MI seems to be relatively high considering the stable patient presentation and nonurgent nature of PCI. The impact of these biomarker elevations on informed consent process, patient management, length of stay, and so forth, is also not clear. A recent report from the Mayo Clinic (4) indicated that extending hospitalization in these

patients solely on the merits of a minor elevation in cardiac troponin T, in the absence of a significant procedural complication or clinical indications, is unlikely to be beneficial.

Seventh, the association between post-PCI biomarker elevation and in-hospital and long-term adverse clinical outcomes was not provided in this study. Thus, the clinical relevance of these biomarker elevations remains unclear in the current setting. Even if the prognostic implications of post-PCI biomarker elevation were clearly well established, its impact on clinical practice would be predicated on the ability to modify post-PCI biomarker elevation. Several investigations have shown lack of benefit on infarct size, left ventricular function and remodeling, or clinical outcome with distal protection devices in patients with acute coronary syndromes. It is possible that distal protection devices could be of potential clinical benefit in carefully selected patients in whom high-risk plaques are identified by VH-IVUS. Similarly, selected high-risk patients might potentially benefit from more aggressive antithrombotic strategies, including higher doses of clopidogrel or glycoprotein IIb/IIIa inhibitors or newer agents such as prasugrel, although further studies are warranted to substantiate this hypothesis.

Notwithstanding these limitations, the information provided by the study of Hong et al. (7) coupled with previous reports supports the rationale behind the hypothesis of using tissue characterization to identify patients at higher risk of distal embolization and myonecrosis after stenting. These observations need to be validated prospectively in larger cohorts of patients before routine use of VH-IVUS technology in clinical practice can be justified. Biomarker elevations in the setting of PCI indeed are messages from the heart. Someday we will more firmly link these messages with the underlying spectrum of plaque morphology—*The Rainbow Connection*. The current study is an important step in that direction.

Reprint requests and correspondence: Dr. Sanjay Kaul, Division of Cardiology, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048. *E-mail: kaul@cshs.org.*

REFERENCES

1. The Rainbow Connection. Available at: http://www.lyricsdownload.com/kermit-the-frog-the-rainbow-connection-lyrics.html. Accessed March 7, 2009.
2. Antman EM, Morrow DA. Biomarker release after percutaneous coronary intervention: a message from the heart. Circ Cardiovasc Interv 2008;1; 3–6.
3. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28: 2525–38.
4. Prasad A, Rihal CS, Lennon RJ, Singh M, Jaffe AS, Holmes DR Jr. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: an analysis of preintervention and postintervention troponin T levels in 5487 patients. Circ Cardiovasc Intervent 2008;1: 10–9.
5. Bolognese L, Ducci K, Angioli P, et al. Elevations in troponin I after percutaneous coronary interventions are associated with abnormal tissue-level perfusion in high-risk patients with non-ST-segment-elevation acute coronary syndromes. Circulation 2004; 110:1592–7.
6. Selvanayagam JB, Porto I, Channon K, et al. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. Circulation 2005; 111:1027–32.
7. Hong YJ, Mintz GS, Kim SW, et al. Impact of plaque composition on cardiac troponin elevation after percutaneous coronary intervention: an ultrasound analysis. J Am Coll Cardiol Img 2009;2:458–68.
8. Kawaguchi R, Oshima S, Jingu M, et al. Usefulness of virtual histology intravascular ultrasound to predict distal embolization for ST-segment elevation myocardial infarction. J Am Coll Cardiol 2007;50:1641–6.
9. Nakamura T, Kubo N, Ako J, Momomura S. Angiographic no-reflow phenomenon and plaque characteristics by virtual histology intravascular ultrasound in patients with acute myocardial infarction. J Interv Cardiol 2007; 20:335–9.
10. Kawamoto T, Okura H, Koyama Y, et al. The relationship between coronary plaque characteristics and small embolic particles during coronary stent implantation. J Am Coll Cardiol 2007;50:1635–40.
11. Uetani T, Amano T, Ando H, et al. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. Eur Heart J 2008; 29:1714–20.