Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Paradigm Shift From Myocardium-Derived to Plaque-Derived Biomarkers for Very Early Diagnosis of Acute Myocardial Infarction

Takuroh Imamura, MD, PhD

A diagnosis of acute myocardial infarction (AMI) is based on prolonged chest pain, electrocardiographic changes and elevated serum creatine kinase (CK) levels. Besides CK, serum levels of heart-type fatty acid-binding protein (H-FABP), myoglobin, troponin T or I, and CK-MB can also provide support for a diagnosis of AMI. These biomarkers are released from damaged cardiomyocytes into circulating blood and they are indicative of acute myocardial injury. The European Society of Cardiology and the American College of Cardiology Consensus group recently emphasized the diagnostic value of troponins as biomarkers of myocyte necrosis.[1] Although troponin T or I is a more sensitive and specific biomarker of myocardial necrosis than either CK or CK-MB, serum levels of troponin T or I start to increase between 2 and 4 h after AMI onset. Accordingly, blood samples obtained from patients with AMI upon arrival at an emergency department are occasionally negative for troponins.[2] Nonetheless, the appropriate treatment must be selected for patients with AMI as soon as possible in a clinical emergency. The appearance of earlier diagnostic biomarkers suggestive of AMI might allow cardiologists to apply expeditious reperfusion therapy under emergency circumstances. Since plaque rupture or erosion with subsequently occlusive thrombus formation is considered the main mechanism responsible for AMI, a novel biomarker derived from ruptured or erosive plaque might be useful for the very early diagnosis of AMI rather than a biomarker derived from the myocardium with ischemic damage. Since biomarkers derived from ruptured or erosive plaque are not direct indicators of myocardial necrosis, a diagnosis of AMI eventually requires an increase in the serum level of a biomarker derived from the necrotic myocardium.

Article p 1433

Initially identified in aortic endothelial cells, lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1) is a receptor for oxidized LDL and a single transmembrane protein belonging to the C-type lectin family.[3] LOX-1 has a short N-terminal cytoplasmic domain, a transmembrane domain and a long C-terminal extracellular domain that consists of a neck and a C-type lectin-like domain that binds oxidized LDL.[3] LOX-1 is expressed in luminal endothelial cells of early human atherosclerotic lesions, but is more predominant in macrophages and smooth muscle cells in the intima of early and advanced human atherosclerotic plaques.[4] Various stimuli, such as oxidized LDL, fluid shear stress, angiotensin II, tumor necrosis factor-α, transforming growth factor-β, homocysteine, C-reactive protein (CRP), interleukin (IL)-6, IL-1α, IL-1β, remnant-like lipoprotein particles, high glucose and advanced glycation endproducts, can induce LOX-1 expression.[5] LOX-1 is also expressed in human platelets and increased in activated platelets.[6] Immunohistochemical staining for LOX-1 has been identified in thrombus associated with atherosclerotic plaque obtained from a patient with unstable angina.[6] Based upon these findings, LOX-1 is considered to be involved in platelet activation and thrombus formation after plaque erosion or rupture that results in acute coronary syndrome (ACS). As far as I can ascertain, no reports have yet identified more LOX-1 in the coronary plaques of patients with than without ACS. However, its expression is reportedly associated with histologically vulnerable atherosclerotic plaque in hypercholesterolemic rabbits.[7] LOX-1 also contributes to the apoptosis of endothelial and smooth muscle cells and is implicated in the oxidized LDL-induced expression and activation of matrix metalloproteinases (MMPs).[8] These findings suggest an intimate relationship between LOX-1 expression and atherosclerotic plaque destabilization.

LOX-1 is cleaved from the cell surface by specific proteases, one of which could be a disintegrin and metalloproteinase (ADAM)10, and released as soluble LOX-1 (sLOX-1).[9] Release of sLOX-1 via the ADAM10 pathway could be stimulated by IL-18, which is increased in the plasma of patients with ACS.[10] In fact, circulating sLOX-1 levels are significantly elevated during the acute stage of ACS, but not in stable coronary artery disease.[11] LOX-1 expression is also induced in cardiac myocytes by stimulation with norepinephrine and endothelin-1, and it is upregulated in the failing rat heart, which suggests that cardiac myocytes might be another source of sLOX-1 release.[5] However, since sLOX-1 does not correlate with troponin T or CK levels in patients with ACS, sLOX-1 might not be a biomarker of myocardial necrosis.[11] Thus, LOX-1 expression is considered to be upregulated in vulnerable plaque, and the cleavage and release process of sLOX-1 via the ADAM10 pathway could be enhanced in pa-

Received April 8, 2011; accepted April 10, 2011; released online April 27, 2011
Department of Internal Medicine, Division of Circulatory and Body Fluid Regulation, Faculty of Medicine, Miyazaki University, Miyazaki, Japan
Mailing address: Takuroh Imamura, MD, PhD, Department of Internal Medicine, Division of Circulatory and Body Fluid Regulation, Faculty of Medicine, Miyazaki University, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan. E-mail: imatak@med.miyazaki-u.ac.jp
ISSN-1346-9843 doi:10.1253/circj.CJ-11-0382

tients with ACS, suggesting that elevated circulating sLOX-1 reflects plaque vulnerability or rupture in such patients. Serum levels of sLOX-1 could be a useful biomarker for an early diagnosis of ACS. The prognostic value of sLOX-1 after ACS has also been reported.[12] Inflammation, the immune response, oxidative stress, apoptotic cell death, MMP modulation and intraplaque hemorrhage are considered relevant mechanisms in plaque vulnerability and rupture. Therefore, various proinflammatory cytokines or plaque destabilization factors have been considered as candidate surrogate markers of plaque vulnerability, such as CRP, IL-6, IL-18, MMPs, monocyte chemoattractant protein-1, myeloperoxidase, oxidized LDL, pentraxin 3, pregnancy-associate plasma protein-A, soluble CD163, soluble CD40 ligand, and soluble scavenger receptor for phosphatidylserine and oxidized lipoprotein/CXC chemokine ligand 16.[13,14] Despite the many publications, studies investigating the value of biomarkers for a very early diagnosis of AMI are quite scarce. To date, no biomarker has been established as a rapid, early diagnostic indicator of AMI before myocardial damage becomes apparent.

Kobayashi et al state in this issue of the Journal that circulating sLOX-1 levels are significantly higher in patients with ST and non-ST elevation AMI than in those with non-AMI and that circulating sLOX-1 diagnoses the early stages of ST elevation MI more accurately than H-FABP, myoglobin, troponin T and CK-MB. They also prove that serum sLOX-1 peaks before serum H-FABP, myoglobin, troponin T and CK-MB.[15] The importance of these findings, regardless of the relatively small study population, is that circulating sLOX-1, a biomarker of plaque vulnerability or rupture is more useful than biomarkers of myocardial damage for a very early diagnosis of ST elevation MI. The use of biomarkers to aid the diagnosis of AMI has enabled the identification of patients who require urgent reperfusion.[2] LOX-1 may be a useful biomarker for a rapid diagnosis of AMI and for appropriate therapeutic decision-making, in addition to being a promising candidate biomarker of plaque vulnerability or rupture. Since serum sLOX-1 does not increase in general acute inflammatory states or stable coronary artery disease,[12] it is also useful to rule-out non-ischemic ST elevation cardiac diseases such as acute myocarditis and takotsubo cardiomyopathy. Multicenter trials are required to explore which biomarker, including sLOX-1, is the most valuable for detecting plaque instability before myocardial necrosis in patients with AMI.

References

1. Thygesen K, Alpert JS, White HD; on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation* 2007; **116:** 2634–2653.
2. Yasuda S, Shimokawa H. Acute myocardial infarction: The enduring challenge for cardiac protection and survival. *Circ J* 2009; **73:** 2000–2008.
3. Sawamura T, Kume N, Aoyama T, Moriwaki H, Hoshikawa H, Aiba Y, et al. An endothelial receptor for oxidized low-density lipoprotein. *Nature* 1997; **386:** 73–77.
4. Kataoka H, Kume N, Miyamoto S, Minami M, Moriwaki H, Murase T, et al. Expression of lectinlike oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. *Circulation* 1999; **99:** 3110–3117.
5. Navarra T, Del Turco S, Berti S, Besta G. The lectin-like oxidized low-density lipoprotein receptor-1 and its soluble form: Cardiovascular implications. *J Atheroscler Thromb* 2010; **30:** 317–331.
6. Chen M, Kakutani M, Naruko T, Ueda M, Narumiya S, Masaki T, et al. Activation-dependent surface expression of LOX-1 in human platelets. *Biochem Biophys Res Commun* 2001; **282:** 153–158.
7. Ishino S, Mukai T, Kume N, Asano D, Ogawa M, Kuge Y, et al. Lectin-like oxidized LDL receptor-1 (LOX-1) expression is associated with atherosclerotic plaque instability: Analysis in hypercholesterolemic rabbits. *Atherosclerosis* 2007; **195:** 48–56.
8. Li D, Liu L, Chen H, Sawamura T, Ranganathan S, Mehta JL. LOX-1 mediates oxidized low-density lipoprotein-induced expression of matrix metalloproteinases in human coronary artery endothelial cells. *Circulation* 2003; **107:** 612–617.
9. Murase T, Kume N, Kataoka H, Minami M, Sawamura T, Masaki T, et al. Identification of soluble forms of lectin-like oxidized LDL receptor-1. *Arterioscler Thromb Vasc Biol* 2000; **20:** 715–720.
10. Mitsuoka H, Kume N, Hayashida K, Inui-Hayashiada A, Aramaki Y, Toyohara M, et al. Interleukin 18 stimulates release of soluble lectin-like oxidized LDL receptor-1 (sLOX-1). *Atherosclerosis* 2009; **202:** 176–182.
11. Hayashida K, Kume N, Murase T, Minami M, Nakagawa D, Inada T, et al. Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are elevated in acute coronary syndrome: A novel marker for early diagnosis. *Circulation* 2005; **112:** 812–818.
12. Kume N, Mitsuoka H, Hayashida K, Tanaka M, Kita T. Soluble lectin-like oxidized low-density lipoprotein receptor-1 predicts prognosis after acute coronary syndrome: A pilot study. *Circ J* 2010; **74:** 1399–1404.
13. Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler Thromb Vasc Biol* 2007; **27:** 15–26.
14. Hochholzer W, Morrow DA, Giugliano RP. Novel biomarkers in cardiovascular disease: Update 2010. *Am Heart J* 2010; **160:** 583–594.
15. Kobayashi N, Hata N, Kume N, Seino Y, Inami T, Yokoyama S, et al. Soluble lectin-like oxidized low-density lipoprotein receptor-1 as an early biomarker for ST elevation myocardial infarction: Time-dependent comparison with other biomarkers. *Circ J* 2011; **75:** 1433–1439.