Early detection of acute coronary syndrome (ACS) is extremely important for patients because of the prognostic benefit following timely intervention. It’s particularly challenging for the emergency physician when the ECG is inconclusive, so specific, sensitive and cost-effective biomarkers have appeared as a promising supplemental diagnostic tool for ACS in the past 2 decades. Measurement of cardiac troponin, natriuretic peptides, creatine kinase-myocardial bound, and C-reactive protein (CRP) levels has been fully incorporated into clinical care for many years. Of them, cardiac troponin (cTn) is considered to be the “gold standard” biomarker because of its myocardial tissue specificity and sensitivity, as well as its established usefulness for therapeutic decision-making. However, even current generation troponin assays have certain limitations. Firstly, cTn is released into the circulation when damage to the myocyte has occurred. Therefore, it is specific for cardiac injury, but myocardial ischemia is not specific for ACS. Patients with pulmonary embolism, hypertensive emergency or sepsis can have an increased level of plasma troponin. Over-reliance on troponin may mislead the further diagnosis and treatment. Secondly, the maximal sensitivity of the standard troponin assay is not achieved until 6 or more hours after the initiation of myocardial necrosis, which indicates its insufficient sensitivity for early detection of ACS. Recently, newer generations of highly-sensitive troponin assays are being developed to overcome that limitation. However, the newer assays demonstrate low-level cTn positively in apparently healthy people or in patients who do not have a final diagnosis of ACS. Taken together, these results highlight the importance of developing a complimentary biomarker specifically targeting early-stage ACS.

Matrix Metalloproteinase-9 vs. Troponin T – The Sooner the Better? –

Wei Kong, MD, PhD

In this issue of the Journal, Kobayashi et al demonstrate that matrix metalloproteinase-9 (MMP-9) shows superiority over high-sensitivity troponin T (hs-TnT) in diagnosing early-stage ACS. MMP-9 belongs to the zinc-dependent endopeptidases MMP family. To date, 23 MMPs have been described in humans and at least 14 of them have been identified in vascular tissues. They are able to degrade most of the constituents of extracellular matrix (ECM) in vessels or to generate other products that have biological consequences. In addition, MMPs also cleave, activate or inactivate a variety of non-ECM proteins, including cytokines, chemokines, and growth factors. Therefore, MMPs have been suggested as a promising diagnostic biomarker or therapeutic target for atherosclerosis, plaque rupture, restenosis and other cardiovascular diseases, by interfering with the process of cell proliferation, migration, invasion, inflammation, angiogenesis, apoptosis, and plaque vulnerability. Existing experimental data strongly suggest that MMP-9 activity could facilitate the formation of atherosclerosis, plaque destabilization and rupture, as well as thrombocyte aggregation. Although large morbidity and mortality trials are still required, epidemiological study to date supports the value of plasma MMP-9 in predicting plaque destabilization and rupture. The latter is believed to appear before acute myocardial infarction. Kobayashi et al. have shown that although both MMP-9 and TnT are elevated in ACS, compared with a control group, within 4 h of ACS onset only the plasma level of MMP-9 was markedly elevated and that of TnT was not significantly altered. Additionally, MMP-9 levels were significantly higher in patients with early ACS than with late ACS either with or without ST segment elevation. In contrast, levels of hs-TnT were significantly lower in patients with early ACS than with late ACS. The plausibility of this study is further based on their time-course study comparing the value of MMP-9 vs. TnT in predicting early-stage ACS. Their study indicates that plasma levels of MMP-9 are elevated approximately 80 min after the onset of ACS and sustained for 24 h thereafter, whereas serum levels of hs-TnT peaked at 12–24 h after arrival at the emergency room. MMP-9 may therefore serve as complimentary diagnostic biomarker in addition to the cardiomyocyte necrosis marker, TnT.

Besides TnT and MMP-9, there are literally dozens of biomarkers that have been reported to be elevated in patients with ACS, such as ischemia-modified albumin (IMA), myeloperoxidase, growth differentiation factor-15, lipoprotein-associated phospholipase A2, soluble CD40 ligand, heart-type fatty acid binding protein (H-FABP), pregnancy-associated plasma protein A etc. In addition, with the advance in proteomic, metabolic and genomic technologies, more and more novel biomarkers have emerged. Nevertheless, priority over existing biomarkers must to be confirmed before these novel biomarkers are widely integrated into clinical practice. In fact, some of the markers have lost their prognostic value after comparison with the sensitivity of cTn. The specificity of diagnostic biomarkers largely affects clinical decision-making. For exam-
ple, MMP-9 has also been suggested to be elevated in aneurysmal disease.\textsuperscript{10} It is therefore important to clarify the time course or plasma concentration of MMP-9 between ACS and aneurysmal rupture/dissection. In addition, a multi-biomarker strategy has exhibited advantage over single biomarker diagnosis of ACS. For example, a combined test for high-sensitivity cTn and H-FABP or IMA has greater diagnostic yield in the early diagnostic assessment of suspected ACS patients.\textsuperscript{13} Large-scale, prospective, randomized clinical trials are needed to test whether a combination of MMP-9/troponin or other novel markers and their combination show greater value in terms of diagnosis, risk stratification, and guiding the treatment and therapy evaluation of ACS.

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Disclosures

None.

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