Cardiac biomarkers for acute coronary syndrome and ongoing myocardial damage in heart failure

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The growing role of cardiac markers has been elucidated in patients with acute coronary syndrome, heart failure and other cardiovascular diseases.

The markers can be cytosolic like heart-type fatty-acid-binding protein (H-FABP) and creatine kinase MB (CKMB), myofibrillary like troponin T (TnT) and cardio-endocrine like B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP).

The usefulness of a point-of-care TnT test is compared with the usefulness of a point-of-care H-FABP test in patients with suspicious acute coronary syndrome. The importance of BNP or NT-proBNP measurements in acute coronary syndrome (NSTEMI) is discussed based on large-scale clinical trials and our investigation.

Progressive deterioration of ventricular function is common in patients with severe chronic heart failure. H-FABP and TnT are markers of ongoing myocardial damage and are associated with subsequent cardiac events in patients with chronic heart failure. The significance of detection of ongoing myocardial damage in chronic heart failure is discussed.

Acute coronary syndrome

Acute coronary syndrome (ACS) is characterized by abrupt plaque rupture and exposure of substances that promote platelet activation and thrombin generation. The resultant thrombus interruption of coronary blood flow results in myocardial necrosis.

An abrupt rupture or erosion of the vulnerable plaque with complete occlusion of blood flow by a so-called red thrombus results in ST-elevation myocardial infarction (STEMI). Less obstructive thrombi and those that are constituted by less robust fibrin formation and

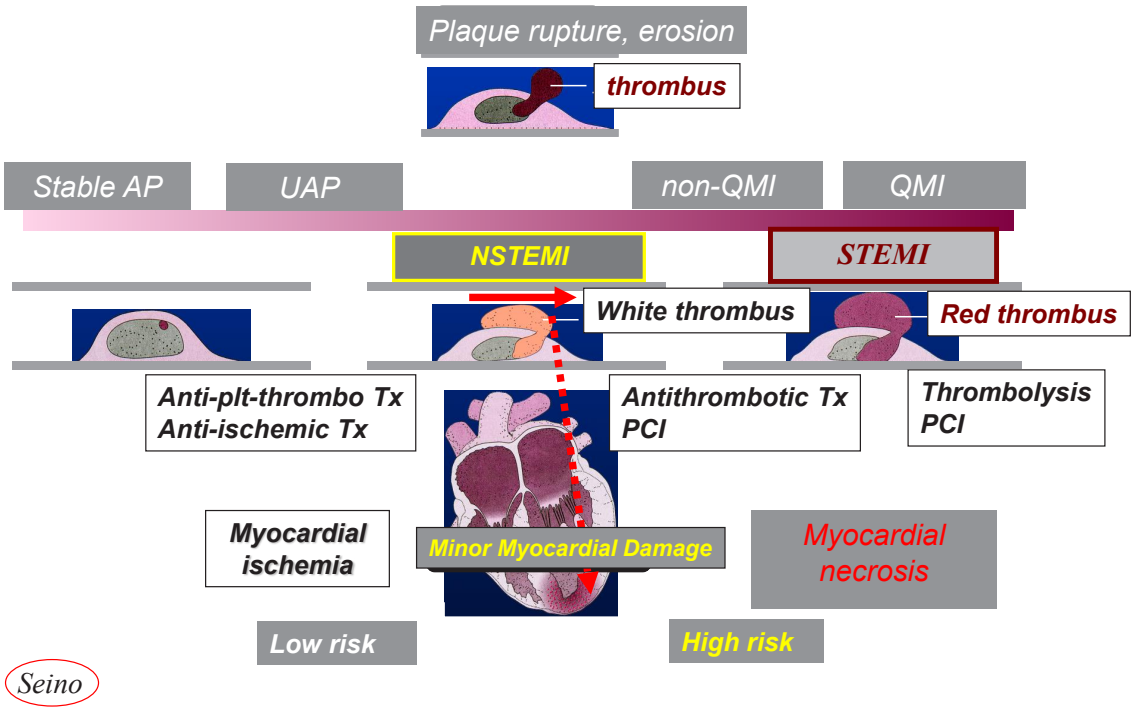

FIGURE 1: Evolving Ischemic Myocardial Damage in ACS - In case of an abrupt rupture or erosion of such vulnerable plaque, complete occlusion of blood flow by red thrombus results in STEMI, and less obstructive thrombi and those that are constituted by less robust fibrin formation and a greater proportion of platelets aggregates, namely white thrombus produce NSTEMI. It is also noticeable that the therapeutic algorithm does differ for the two pathophysiologies.

a greater proportion of platelets aggregates, so-called white thrombus, result in non-ST-elevation myocardial infarction (NSTEMI) (Fig. 1).

It is noticeable that the therapeutic algorithm does differ for these two different spectrums.

Cardiac biomarkers for acute coronary syndrome

The growing role of cardiac markers has been elucidated in patients with acute coronary syndrome, heart failure and other cardiovascular diseases.

The markers can be cytosolic like heart-type fatty-acid-binding protein (H-FABP) and creatine kinase MB (CKMB), myofibrillary like troponin T (TnT) and cardio-endocrine like B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) [1-5].

At present, these three groups of cardiac biomarkers are applied for detection of myocardial damage and the earlier diagnosis of acute coronary syndrome.

Our earlier investigation revealed that measurements of cardiac troponin T detected the presence of minor myocardial damage in patients with unstable angina, even when CKMB was not significantly elevated [1, 2], and those with minor myocardial damage showed higher risk for cardiac events (acute myocardial infarction, cardiac death, or necessity of emergency coronary revascularization) in the acute phase compared with those without minor myocardial damage [1-2].

In 2007, myocardial infarction was completely redefined based on clinical presentation, ECG findings and the elevation of cardiac troponin (using a troponin assay with an acceptable imprecision) instead of conventional CKMB measurements [6].

Troponin t and H-FABP rapid strip test for earlier diagnosis of myocardial infarction

We developed a whole-blood rapid strip test for H-FABP and demonstrated the clinical utility for earlier diagnosis of myocardial infarction [3]. The diagnostic sensitivity and negative predictive value of the rapid H-FABP test were superior compared with those of a rapid TnT test, especially in the earlier-acute phase within 2 to 3 hour of onset of symptoms [3].

Importance of BNP or NT-proBNP measurement in ACS

Large-scale clinical trials have demonstrated that BNP and NT-proBNP are increased in the early stage in acute coronary syndrome and can be used as powerful predictors of short- and long-term mortality. We have revealed different profiles of BNP (NT-proBNP) elevations between STEMI and NSTEMI [8].

The levels of conventional myocardial necrosis markers (CKMB and TnT) were on admission significantly higher in the STEMI group compared with the NSTEMI group [7]. However, conversely, NT-proBNP on admission was significantly higher in the NSTEMI group compared with the STEMI group, especially in the earlier phase.

When the correlation between TnT and NT-proBNP was analyzed and compared between STEMI and NSTEMI groups, the difference revealed augmented elevation of NT-proBNP in the NSTEMI group as compared with prominent elevation of TnT in the STEMI group, indicating development of larger ischemic insult despite of the smaller myocardial necrosis in NSTEMI compared with the STEMI group [7].

Data from FRISC trial [8] and also a substudy of PRISM [9] showed that NT-proBNP levels are highest on admission, within 24 hours of onset, decreased markedly the first 24 hours and then gradually over the following 6 months.

Interestingly, the predictive ability of NT-proBNP appears to increase with time, suggesting that persistent elevation is a particularly strong marker of adverse outcome. A second BNP or NT-proBNP value at 72 hours following the admission appeared to improve risk prediction concerning the end-point of death or recurrent MI at 30 days.

Regardless of the BNP or NT-proBNP value on admission, a NT-proBNP value > 250 pg/mL, or a BNP value > 80 pg/mL at 72 hours indicated a marked increased risk [8].

Although more data concerning the optimal timing of BNP or NT-proBNP measurements is warranted, it seems reasonable to measure BNP or NT-proBNP on presentation for initial fundamental risk assessment and once more during the sub-acute phase either at hospital discharge or at an early post-discharge outpatient visit for long-term risk assessment.

Ongoing myocardial damage in heart failure

Progressive deterioration of ventricular function is common in patients with severe chronic heart failure. We reported that detection of cardiac troponin T in blood identifies heart failure patients who are at increased risk of cardiac events [10].

Further, we have revealed that H-FABP, which is abundant in the cytosol of cardiomyocytes and, as described above, a sensitive marker of myocardial infarction, increased to a greater extent than TnT levels in heart failure patients who have ongoing myocardial damage [11].

Mean levels of H-FABP were greater in patients with NYHA class III or IV heart failure than in those with NYHA class II. Detection of TnT (≥ 0.02 ng/mL) was also more common in patients with worse heart failure (81 % in class III or IV vs. 43 % in class II (Fig. 2) [11].

Significant correlations were found between H-FABP levels and plasma levels of BNP and norepinephrine. Patients with ongoing myocardial damage (TnT ≥ 0.02 ng/mL or H-FABP ≥ 4.7 ng/mL) were independently associated with subsequent cardiac events (deaths or readmissions because of worsening heart failure) (Fig. 3) [11].

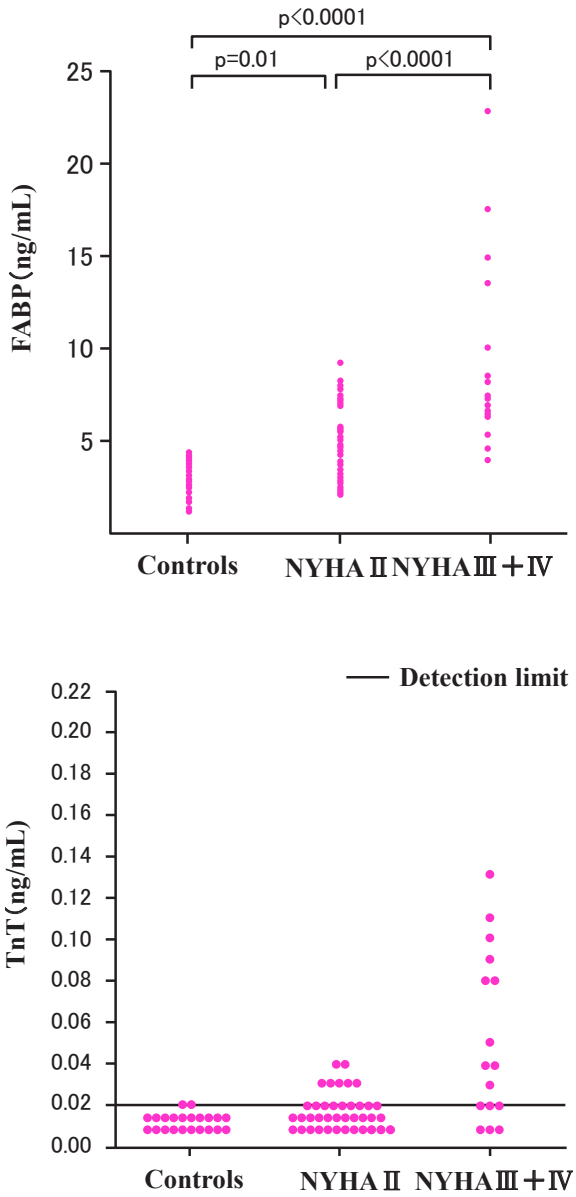

FIGURE 2: Detection of ongoing myocardial damage in chronic heart failure by H-FABP and troponin T measurements.
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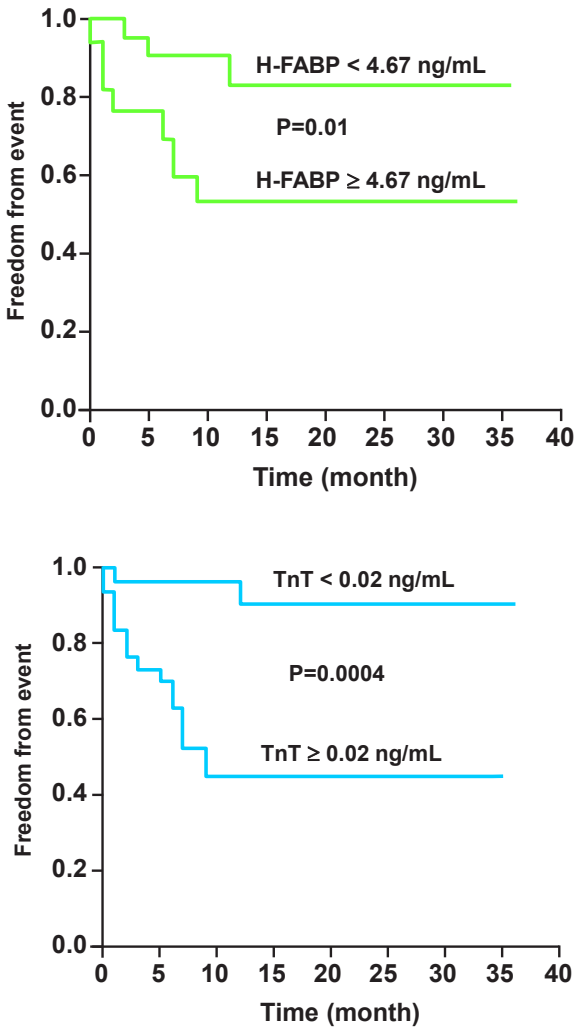

FIGURE 3: Prognostic value of H-FABP and troponin T measurements in chronic heart failure.
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H-FABP and TnT are markers of ongoing myocardial damage and are associated with subsequent cardiac events in patients with chronic heart failure [10, 11].

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