Formación acreditada

VIEWPOINT

Early diagnosis of myocardial injury. What will biochemical markers bring us in the future?

JORDI ORDÓÑEZ LLANOS[1,3], MIQUEL SANTALÓ BEL[2]

[1]Servicio de Bioquímica. [2]Unidad de Semicríticos. Hospital de la Santa Creu i Sant Pau. [3]Departamento de Bioquímica y Biología Molecular. Universitat Autónoma de Barcelona. Barcelona, Spain.

Cardiac troponins in emergency diagnosis

Acute coronary syndrome (ACS) is one of the diseases most frequently treated in the emergency department (ED). Diagnosis is currently based on clinical signs and symptoms, electrocardiography (ECG) and measurement of biomarkers in the blood. Since the early 1990s, the easily measured biomarkers cardiac troponin (cTn) T and I (cTnT, cTnI) have been central to the diagnosis, prognosis, risk stratification and treatment of ACS. There are international recommendations on the use of cTn in ACS, but the recent development of highly sensitive methods for measuring cTn will bring about significant changes in clinical practice. The purpose of this paper is to briefly review what these changes are likely to be, based on existing preliminary data.

Antecedents

Troponin is a component protein of the tropomyosin complex in muscle cells. However, unlike other muscle cell molecules such as myoglobin and creatine kinase (CK) and its MB isoenzyme (CKMB), there are myocardial-specific forms of cTnT and cTnI. The cardiac-specific nature of cTn explains why it has become the biomarker of choice for the evaluation of ACS[1].

The first analytical methods for measuring cTn were described in the early 1990s[2,3], but only relatively high concentrations of cTn could be measured at that time (eg 0.10 µg/L for cTnT or 0.40 µg/L for cTnI). Since then, research has focused on developing methods to measure increasingly lower concentrations with analytical precision, and the methods currently in use allow measuring concentrations 10-20 times lower. Improved analytical sensitivity (the minimum amount measurable) has resulted in improved diagnostic sensitivity, and cTn can now be detected in a greater number of patients with ACS. This has improved the diagnosis of ACS, but paradoxically it has also has promoted the idea that there are "false positives" for cTn in patients without ACS.

As mentioned, cTn is a cardiomyocyte-specific molecule, and its low molecular mass allows easy incorporation into the bloodstream under conditions of even minimal cell alteration (eg. hypoxia-ischemia, which alters cell membrane permeability.) Consequently, not only myocardial necrosis but any condition producing cardiomyocyte damage can cause increased levels of circulating cTn. Table 1 shows a list of conditions under which increased levels of circulating cTn are detected. In these cases the increase of cTn is a "true positive indicator" of myocardial damage, but the origin may not be coronary ischemia. Being aware of this circumstance, scientific societies have always recommended that acute myocardial infarction (AMI) should only be diagnosed where elevated cTn coincides with a clinical setting of coronary ischemia[1,4].

Most of the conditions set out in Table 1 cause sustained elevation of cTn, unlike those found in ACS which show a pattern of rising and falling cTn. The most recent clinical guidelines recommend that, in order to rule out other causes of sustained cTn elevation, the diagnosis of AMI should be based not only on cTn levels above the 99th percentile of reference values, but also on

CORRESPONDENCE: Dr. Jordi Ordóñez Llanos. Servicio de Bioquímica. Hospital de la Santa Creu i Sant Pau. Avda. Sant Antoni Mª Claret, 167. 08025 Barcelona, Spain. E-mail: jordonez@santpau.cat

RECEIVED: 1-6-2010. **ACCEPTED:** 7-6-2010.

CONFLICT OF INTEREST: Drs. Ordóñez Llanos and Santaló Bel declare that they receive and have received financial support for research and conference fees from Abbott Diagnostics, Inverness Medical, Roche Diagnostics and Siemens Medical, which are commercial enterprises that market methods for the measurement of troponin.

Table 1. Causes of elevated troponin in the absence of coronary ischemia

Cardiac causes
1. Underlying causes of myocardial damage:
– Radiofrequency ablation
– Cardiac amyloidosis
– Cardioversion
– Closure of atrial septal defect
– Cardiac Surgery
– Cardiac contusion
– Implantable defibrillator discharge
– Percutaneous coronary intervention
– Myocarditis
– Pericarditis
– Heart transplantation
– Supraventricular tachycardia
– Coronary vasospasm
2. Causes leading to increased heart size:
– Left ventricular hypertrophy
– Heart failure
– Dilated cardiomyopathy
– Hypertrophic cardiomyopathy
Non-cardiac causes
1. Alterations in organs:
– Pulmonary Edema
– Pulmonary embolism
– Subarachnoid hemorrhage
– Primary Pulmonary Hypertension
– Stroke
– Chronic renal failure
2. General disorders:
– Intense aerobic exercise
– Patients in critical condition
– High-dose chemotherapy
– Sepsis and septic shock
– Treatment with sympathomimetics
Methodological reasons
– Interference by heterophile antibodies
– Interference by rheumatoid factor
– Coagulated samples

patterns of increase or decrease in cTn. The greater the sensitivity of the analytical method used to measure cTn, the more accurately will it distinguish patients with levels above the 99th percentile of reference values and thus more easily recognize the existence of changing (rise or fall) cTn concentrations.

Optimal analytical sensitivity is the goal of the so-called "ultra-sensitive" methods of measuring cTn.

Ultrasensitive troponin. Impact on clinical practice

Although not yet systematically commercialized, there are highly sensitive analytical methods that detect cTn concentrations 2-5 times lower than those currently detected, and these methods are called "ultra-sensitive cTn (us-cTn). The ability to detect minute concentrations of cTn will have varying consequences for clinical use depending on the type of patients or condition that they present.

In reference subjects

With ultra-sensitive methods, cTn is detected in 95% or more of reference subjects, whereas current methods detect cTn in no more than 50%.

Tn levels in reference subjects are in the range of 3-20 ng/L (0.003 to 0.020 µg/L) depending on whether it is cTnI-us or cTnT-us that is being measured, and differences between men and women have been detected for both[5,6]. Current methods of measuring cTn show higher values in the elderly and in subjects with cardiovascular risk factors[7]; so these findings are likely to be even more evident with us-cTn.

Since the 99th percentile of reference values is used to define AMI, the selection of subjects to be included in the reference population is critical. Ideally they should be subjects without cardiovascular risk factors or subclinical cardiovascular disease, and with an age and sex distribution similar to the ACS population to be assessed.

In patients with acute coronary syndrome

In patients with low-intermediate risk of ACS, ultra-sensitive methods have detected admission concentrations of cTnT and cTnI above the 99th percentile in about 60-70%. In these same patients, non-ultrasensitive methods only detected such concentrations in 10% of cases[8,9]. The practical consequence of this finding is that the period of time needed to detect abnormal cTn values is significantly reduced; in one study this reduction was nearly 3 hours[10].

In patients with low-intermediate risk of ACS, admission cTnT using an ultra-sensitive method has shown a sensitivity of 62% and specificity of 89% in identifying ACS, compared with 35% sensitivity and 99% using non-ultrasensitive methods specificity in these same patients. Ultra-sensitive cTnT detected 27% more cases of ACS[11]; a 27% decrease of subjects diagnosed with unstable angina was recorded.

An unresolved diagnostic challenge is to recognize the existence of cardiac ischemia that is not clinically evident; diagnosis is usually based on induced ischemia ergometric tests. The increase in ultrasensitive cTnI during exercise testing has proved to be an independent predictor of coronary ischemia assessed by imaging techniques. Neither the duration of the test, ST segment depression or the existence of limiting angina showed any signi-

ficant predictive value[12]. In this study, ultrasensitive cTnI remained unchanged during stress testing in patients who did not develop ischemia and increased by 24% and 40% in patients who developed mild and moderate-severe ischemia, respectively. Current methods do not detect significant increases in cTn during ergometric tests. These data suggest that ultrasensitive Tn could be a marker of ischemia and question the usefulness of other biomarkers proposed to detect it, such as ischemia-modified albumin or choline.

In stable coronary artery disease

Significant increases of ultrasensitive cTnT have been reported, above the 99th percentile in 11% of patients with apparently stable coronary heart disease (CHD). Notably, as in reference subjects, cTnT levels were higher in men than in women[13]. They have been related to complications such as cardiovascular death, fatal or non-fatal congestive heart failure (CHF), and death from non-CHF cardiovascular causes. In another group of patients, elevated ultrasensitive cTnT was associated with the existence and severity of CHD and left ventricular mass, reduced ejection fraction and regional heart dysfunction, evaluated by imaging techniques[11]. These data suggest that ultrasensitive cTn could prove useful for risk stratification in patients with stable CHD[13].

Conclusions

Ultrasensitive cTn will most probably change current methods of diagnosing ACS. The study of these biomarkers is still in its infancy, but it appears that this cTn measure will increasingly be used in cases of chest pain and suspected AMI, but not in patients with unstable angina. Its greater analytic sensitivity will probably mean increased use in non-coronary patients. The differentiation between coronary ischemia and other diseases will be based on patterns of evolutionary change in ultrasensitive Tn values. In any case, the detection of cTn is synonymous with myocardial damage and, consequently, increased cardiovascular risk. It is clear that clinical and laboratory data will be combined to address the challenge of optimizing the use of these biomarkers in ED clinical practice.

References

1 Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined —a consensus document of the joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000;36:959-69.

2 Gerhardt W, Katus H, Ravkilde J, Hamm C, Jørgensen PJ, Peheim L, et al. S-Troponin T in suspected ischemic myocardial injury compared with mass and catalytic concentrations of S-Creatine kinase isoenzyme MB. Clin Chem. 1991;37:105-11.

3 Adams 3d JE, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation. 1993;88:101-6.

4 Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J. 2007;28:2525-38.

5 Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, Van Dieijen-Visser M. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. Clin Chem. 2009;55:101-8.

6 Apple FS, Murakami MM, Farris DP, Karimi SA, Simpson PA, Le LT. Serum 99th percentile reference value for the high sensitive Singulex cardiac troponin I assay. Clin Chem. 2009;55 Suppl:A63.

7 Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation. 2006;113:1958-65.

8 Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem. 2010;56:642-50.

9 Wilson SR, Sabatine MS, Braunwald E, Sloan S, Murphy SA, Morrow D. Detection of myocardial injury in patients with unstable angina using a novel nanoparticle cardiac troponin I assay: Observations from the PROTECT-TIMI 30 Trial. Am Heart J. 2009;158:386-91.

10 Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus AH. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010;56:254-61.

11 Januzzi Jr JL, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, et al. High-sensitivity troponin T concentrations in acute chest ain patients evaluated with cardiac computed tomography. Circulation. 2010;121:1227-34.

12 Sabatine MS, Morrow DA, De Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J. 2009;30:162-9.

13 Omland T, De Lemos JA, Sabatine MS, Christophi CA, Murguia-Rice M, Jablonski KA; for the Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) trial investigators. Sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361:2538-47.