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Review

The exciting story of cardiac biomarkers: From retrospective detection to gold diagnostic standard for acute myocardial infarction and more☆

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Abstract

This paper reviews the history of the contribution of the laboratory medicine to clinical cardiology and discusses the most important steps in this field. Until 20 years ago, the clinical laboratory only placed at the cardiologist's disposal a few assays for the retrospective detection of cardiac tissue necrosis, such as enzymatic methods for creatine kinase and lactate dehydrogenase activities. However, in the latter part of the 20th century, highly sensitive and specific assays, such as cardiac troponins, as well as assays for markers of myocardial function, such as cardiac natriuretic peptides, rapidly changed the scenario of clinical management of patients with cardiac diseases, assigning to the laboratory a pivotal role in the overall diagnostic flow. This is witnessed by the recent incorporation of these markers into international guidelines and in the redefinition of myocardial infarction. For the foreseeable future, new serum markers of myocardial ischemic, i.e. reversible, injury or related to coronary plaque instability and disruption are expected.

Contents

Abbreviations: AST, aspartate aminotransferase; AMI, acute myocardial infarction; LD, lactate dehydrogenase; CK, creatine kinase; WHO, World Health Organization; RIA, radioimmunoassay; ECG, electrocardiogram; cTnT, cardiac troponin T; cTnI, cardiac troponin I; ACS, acute coronary syndrome; ESC, European Society of Cardiology; ACC, American College of Cardiology; CNP, cardiac natriuretic peptides; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; NT-proANP, amino-terminal fragment of proANP; NT-proBNP, amino-terminal fragment of proBNP; CHF, chronic heart failure; MLC, myosin light chains.

☆ To celebrate the 50th anniversary of CCA, a number of invited review papers have been brought together, dealing with important research fields where CCA publications have contributed to the scientific exploration.

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1. Cardiac specificity: like the search of the Holy Grail?

The term "specificity" is generally defined as the quality or attributes relating to one particular thing [1]. In biology and clinical biochemistry, one should distinguish the "analytical specificity", referring to the ability of an assay to measure in biological samples a well defined molecule or substance, i.e. an analyte, rather than others, from the "diagnostic specificity", statistically the percentage of individuals not having a given condition who are correctly identified by an assay as negative for that condition [2]. Focusing on laboratory testing, the analytical specificity of a biochemical marker depends not only on avoiding any methodological crossreactivity with other biologically related molecules, but also on biological characteristics of the marker as well, showing no other tissue sources, even in trace amounts or under pathological conditions, in addition to the anatomic or histologic target.

For biochemical markers of myocardial injury, for which the target organ is the heart, the cardiac specificity is of pivotal importance, even crucial for their clinical application [3]. Although any molecule candidate to become a successful cardiac biomarker should have certain characteristics, cardiac specificity is the hallmark of the ideal biomarker, because it definitively improves all its diagnostic characteristics, from sensitivity for damage detection to earlier appearance in blood (Table 1). A lower cutoff, close to the detection limit of the method, can be introduced, thus improving diagnostic sensitivity at its best, because also the smallest quantity of analyte different from the analytical noise may reflect a myocardial damage. Furthermore, when the assay is sensitive enough to detect small amounts of the cardiac specific marker, it may give earlier information revealing as rapid as possible the occurrence of myocardial injury. Therefore, it is not surprising that along the story of the search of the "ideal" cardiac biomarker, we are often recording scientists searching for new and even more cardiac specific markers as powerful tools to rapidly and accurately define any myocardial injury (Fig. 1).

Table 1
Characteristics of an ideal cardiac biomarker

High sensitivity
High concentration in myocardium after myocardial injury
Rapid release for early diagnosis
Long half-life in blood for late diagnosis
High specificity
Absent in non-myocardial tissues
Not detectable in blood of non-diseased subjects
Analytical characteristics
Measurable by cost-effective assay
Simple to perform
Rapid turnaround time
Sufficient precision and trueness
Clinical characteristics
Ability to influence therapy
Ability to improve patient outcome

2. The pioneering age

In 1954, Karmen et al. [4] first reported that release of aspartate aminotransferase (AST), formerly glutamate oxaloacetate transaminase, from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of acute myocardial infarction (AMI). Today, we know that this enzyme is fully non-cardiospecific, being ubiquitously found in liver, skeletal muscle, red blood cells, and many other tissues. However, this discovery pioneered other researches related to the determination of enzyme activities in serum used as biochemical detector of myocardial necrosis. In particular, one year later the lactate dehydrogenase (LD) application in AMI diagnosis was described [5]. As LD was, however, found in nearly all human tissues, a direct assay for α-hydroxybutyrate dehydrogenase activity in serum, based on the ability of LD1 (present in high amounts in the heart) and LD2 isoenzymes to oxidize α-hydroxybutyric acid much faster than LD5, was later presented to increase cardiac specificity [6].

In the same years, the first "cardiac" marker, i.e. the creatine kinase (CK) activity in serum, was described, emphasizing its rapid appearance and marked increase in serum after AMI and its specificity for myocardial injury when compared with AST and LD, without otherwise being able to suggest an effective methodology for its clinical application [7]. At that time, the available methods required too much time and high technical skill to be reliably performed in clinical laboratories and seven years passed before an effective coupled enzymatic assay for CK was developed and proposed [8]. The labour involved to optimize the reaction and to combine all reagents in a composition useful to make easy and quick the CK activity measurement was really impressive, as documented by Sydney Rosalki himself, the pioneer scientist who put this cornerstone of the science in the field of laboratory medicine [9]. After three years of work, he was able to prepare a single reagent mixture into gelatine capsules, requiring only aqueous reconstitution and sample addition. It is actually surprising that the same basic reagents, only slightly modified and optimized, are still used in a completely different technical environment, as fully automated clinical chemistry analyzers are [10].

The availability of a simple and reliable method was a starting point for the worldwide use of CK activity measurement in the investigation of heart injury. CK has been the mainstay for diagnosis of AMI for nearly 20 years because of its sensitivity, being one of the most abundant molecules of the myocytes released after cell death, and higher specificity when compared with AST and LD activities. The increase of the CK activity within 4–8 h after the admission of a patient with chest pain related to AMI and the typical release curve during Q-wave AMI, peaking 18–24 h after onset of symptoms before falling to baseline concentrations within 48–72 h, gave to cardiologists the opportunity to make or confirm diagnosis of AMI within 24 h after hospital admission instead of the traditional 2–3 days needed with AST and LD, thus significantly reducing the time for intensive observation.

At the beginning of 1970s, remarkable information, first obtained on animal models, was the demonstration that the extent of myocytes necrosis induced by the infarction largely influenced mortality and morbidity of patients [11]. The application of CK release in quantification of the infarct size and its comparison with the histological estimate showed that CK activity in plasma