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Review article

BIOCHEMICAL MARKERS OF CARDIAC DISEASES

Mauro Panteghini

Clinical Chemistry Laboratory 1, Spedali Civili University Hospital, Brescia, Italy

Summary: This article reviews the current contribution of the determination of biochemical markers to clinical cardiology and discusses some important developments in this field. Biochemical markers play a pivotal role in the diagnosis and management of patients with acute coronary syndrome (ACS), as witnessed by the incorporation of cardiac troponins into new international guidelines for patients with ACS and in the redefinition of myocardial infarction. Despite the success of cardiac troponins, there is still a need for development of early markers that can reliably rule out ACS from the emergency room at presentation and detect myocardial ischemia also in the absence of irreversible myocyte injury. Under investigation are two classes of indicators: markers of early injury/ischemia and markers of coronary plaque instability and disruption. Finally, with the characterization of the cardiac natriuretic peptides, Laboratory Medicine is also assuming part in the assessment of cardiac function.

Key words: biological markers, diagnosis, myocardial infarction, troponin

Introduction

Although its incidence has declined over the recent years with a better understanding of the pathophysiology, widespread implementation of lipid lowering drugs, and improved treatments such as stent placements, cardiovascular disease remains the leading cause of morbidity and mortality in the industrialized world (1). Each year, approximately 2.6 million people die of cardiovascular disease in the United States, Europe and Japan and more than 16 million lives are claimed worldwide. While hypertension is the most common type of cardiovascular disease, acute myocardial infarction (MI) and ischemic heart disease are the most common cause of death contributing to more than 50% of the total deaths (2).

The economic impact of coronary heart disease is also substantial. Its yearly cost in the United States has been estimated to be more than 100 billion dollars, including direct costs, such as the cost of physicians and other professionals, hospital and home services, medications, plus indirect costs attributed to lost productivity from morbidity and mortality (3). One of the main reasons of these elevated costs is that the proper assessment and triage of the patient with suspected acute coronary syndrome (ACS) is a resource-intensive and complex decision-making process (4). Patients with suspected ischemic chest pain represent a major diagnostic challenge, critical to their effective management being the early recognition of a cardiac ischemic event and the proper placement of the patient in the risk spectrum of ACS (5). On the other hand, with the population getting older and more patients are surviving episodes of ACS, the incidence of congestive heart failure (CHF) is growing at a dramatic rate. An estimate of current prevalence of CHF in western countries is around 18 million, with an incidence of approximately 3.8 million new cases each year (6).

In this context, cardiac biomarkers have grown in importance (7, 8). Until 25 years ago, Laboratory Medicine placed at clinical cardiology's disposal only a few assays for the retrospective detection of cardiac tissue necrosis, such as enzymatic methods for creatine kinase (CK) and lactate dehydrogenase catalytic activities (9). However, in the last part of the 20th century, highly sensitive and specific assays for the detection of myocardial damage, such as cardiac troponins, as well as assays for reliable markers of myocardial function, such as cardiac natriuretic peptides (CNP), have become available, assigning to the laboratory a pivotal role in the diagnosis and follow-up of patients with cardiac

Address for correspondence:

Professor Mauro Panteghini
Clinical Chemistry Laboratory 1
Spedali Civili University Hospital, 25125 Brescia, Italy.
Tel: +39 030 3995470; fax: +39 030 3995369.
E-mail address: panteghi@bshosp.osp.unibs.it

disease, as witnessed by the recent incorporation of these markers into new international guidelines and in the redefinition of MI (10–14). The aim of this article is to review the current contribution of the determination of biochemical markers to clinical cardiology and discuss some important developments in this field.

The detection of myocardial necrosis

In September 2000, the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) committee published its consensus recommendations for a new definition of MI (14). While the previously used World Health Organization (WHO) definition required the presence of at least two of three criteria, namely, an appropriate clinical presentation, typical changes at electrocardiogram (ECG) and raised »cardiac« enzymes, essentially total CK or its MB isoenzyme (CK-MB) activities, the ESC/ACC definition of acute MI requires the rise and fall of the biochemical marker of myocardial necrosis together with one of criteria, comprising ischemic symptoms, the development of pathologic Q waves, ischemic ECG changes or a coronary artery intervention (14, 15). Thus, according to the traditional WHO definition, an acute MI could be diagnosed without biochemical evidence of myocardial necrosis, while the ESC/ACC criteria mandate that the biomarkers be elevated and, subsequently, be shown to fall in the appropriate clinical context (14).

Quite simultaneously, other expert committees published companion documents, where in patients with ischemic symptoms but no ST-segment elevation at ECG, a positive cardiac troponin result identifies patients who have non-ST-segment elevation myocardial infarction (NSTEMI) and who could benefit from aggressive medical therapy (10, 11).

The new consensus documents have therefore based the new definition of MI on biochemical grounds, a choice that was guided by the advent of new markers of myocardial necrosis, such as cardiac troponins (16–18). The superior troponin's clinical value comes from its higher sensitivity to smaller myocardial injury and its virtually total specificity for cardiac damage (17). Despite the ability to detect quantitatively smaller degrees of myocardial necrosis, cardiac troponins need 4 to 10 hours after symptom onset to appear in serum, at about the same time as CK-MB elevations become detectable, and peak at 12 to 48 hours, remaining then abnormal for several days (19). There is however a relationship between the severity of the infarct and the duration of the elevation of troponins in the serum (7). The release periods of troponin in patients with NSTEMI are significantly less than those with ST elevation at ECG, and troponin elevations in traditionally defined unstable angina patients, representing microscopic infarct, might last only several hours at a time (20).

In applying the results of cardiac troponin testing to the defining of MI, one should keep in mind that these markers actually reflect myocardial necrosis but do not indicate its mechanism. Thus, an elevated value in the absence of clinical evidence of ischemia should prompt a search for other causes of cardiac damage. Many nonischemic pathophysiological conditions can cause myocardial necrosis and therefore elevations in cardiac troponin concentrations (*Table I*) (21–43). The occurrence of myocardial damage in clinical contexts other than MI frequently obliges physicians to determine whether such damage occurs in the clinical setting of acute myocardial ischemia, thus leading to the diagnosis of MI, or not (44). Strictly speaking, even in the »troponin era«, the diagnosis of MI remains clinical. Measurement of cardiac troponin provides a valuable diagnostic test for MI only when used together with other clinical informations. In particular, to satisfy the diagnostic criteria for MI, troponin elevations should be accompanied by objective instrumental evidence that myocardial ischemia is the likely cause of myocardial damage especially when only one marker measurement is available and its characteristic release kinetics cannot be demonstrated or when marker changes are not consistent with the onset of symptoms or remain stable over time (45). Ideally, three measurements of cardiac troponin are suggested, with a sampling frequency of hospital admission, 6 hours and 12 hours after, to demonstrate changing values (46). This biochemical strategy can readily show if the temporal variations in the troponin concentrations in serum are consistent with the onset of symptoms and may very often obviate the need for subsequent extensive confirmation testing, such as imaging techniques.

Table I Nonischemic cardiac diseases causing elevation of cardiac troponins in serum

- Acute rheumatic fever
- Amyloidosis
- Cardiac trauma (including contusion, ablation, pacing, firing, cardioversion, catheterization, cardiac surgery)
- Cardiotoxicity from cancer therapy
- Congestive heart failure
- Critically ill patients
- End-stage renal failure
- Glycogen storage disease type II (Pompe's disease)
- Heart transplantation
- Haemoglobinopathy with transfusion haemosiderosis
- Hypertension, including gestational
- Hypotension, often with arrhythmias
- Hypothyroidism
- Myocarditis/Pericarditis
- Postoperative noncardiac surgery
- Pulmonary embolism
- Sepsis

An important issue in the practical use of cardiac troponins is the appropriate definition of decision limits (47). From a clinical perspective, there is evidence that any amount of detectable cardiac troponin release is associated with an increased risk of new adverse cardiac events. Currently available data demonstrate no threshold below which elevations of troponin are harmless and without negative implications for prognosis (48–50). In agreement with the outcome studies, the consensus documents define the myocardial necrosis as an increase of cardiac troponin values exceeding the upper reference limit of the healthy population, set at the 99th percentile of the value distribution to limit the number of false-positive designations of myocardial injury (51). On the basis of current available data, however, it would seem reasonable to expect analytical methods to give an undetectable value or very low troponin value as »normal« (52). None of the commercially available troponin assays has shown acceptable analytical imprecision at these low concentration values to obtain accurate discrimination between »minor« myocardial injury and analytical noise (53). In the context of clinical practice a predetermined higher cardiac troponin concentration that meets the requested goal for desirable imprecision, i.e. a total coefficient of variation (CV) $\leq$10%, should therefore be used as the cut-off for MI until the assays are improved (45, 51, 54). The use of the actual 10% CV troponin concentration instead of the lower 99th percentile reference limit as decision cutoff could slightly decrease the clinical sensitivity of the biochemical criterion used for the MI diagnosis, but should permit physicians to avoid the occasional spurious increase in serum troponin concentrations due to analytical noise (55).

It is well demonstrated that the use of the new, more sensitive diagnostic criteria for MI leads to an average increase of the numbers of infarct patients in the ACS population from 20 to 30% (56, 57). However, the percentage of patients recategorized from angina to MI is also critically dependent on the performance of the troponin assay used. Although higher precision at lower troponin concentrations does not automatically equate with higher clinical sensitivity, the use of a high-sensitivity troponin assay would allow identification of a substantial and additional proportion of patients with MI compared with a less sensitive troponin assay (58).

Decision limits other than the 99th percentile and 10% CV values have been clinically defined for some of the cardiac troponin methods and used for risk stratification of patients with ACS (48, 49). Although the data from these clinical trials are compelling, the use of cardiac troponin for MI diagnosis is different from its use for risk stratification. Differences in the prevalence of ACS in different populations have to be considered. If the purpose of measuring cardiac troponin is only to risk-stratify patients with ACS for adverse events, consideration should be given to lowering the troponin cutoff below the 10% CV value. However, these low troponin cutoffs are not likely appropriate for the diagnosis of MI in a cohort of patients with chest pain and a lower prevalence of disease, where false-positive results produced by a cardiac troponin assay as a result of analytical imprecision could have a much larger negative impact (55).

Early detection of myocardial damage

Some practical aspects for optimizing the sampling protocols and for combining, in case, troponin measurements with other biomarkers in the clinical routine setting still need to be clarified (59). In general, it is important that hospitals tailor their diagnostic strategies for the investigation of patients with suspected ACS to local circumstances and to the way that the test results will be used (60). One appealing approach relies on the use of a combination of two markers – a rapidly rising marker and a marker that takes longer to rise but is more specific, such as cardiac troponin – to enable the detection of MI in patients who seek care early and late after symptom onset (7, 16, 46, 61). This two-marker strategy is predicated on the assumption that early diagnosis will change care by providing the ability to discharge patients earlier, thus improving flow within the emergency department setting, and by facilitating identification of patients who may be candidates for aggressive interventions and, more generally, facilitating the triage of patients who are admitted to various parts of the hospital (62). Myoglobin is the marker that currently most effectively fits the role as an early marker (19). Its concentrations in blood appear quickly, reaching the maximum between 6 and 12 hours after the onset of symptoms. It then falls to normal over the next 24 hours, rapidly cleared from the serum by the kidneys. Myoglobin has, however, low specificity for cardiac necrosis, so that the use of this marker always requires associate cardiac troponin measurements to confirm myocardial injury and eliminate myoglobin false-positives (63). Myoglobin has therefore clinical utility only as test for excluding early MI (64).

Despite the undoubted success of myoglobin for ruling out early myocardial necrosis in suspected patients 4 to 6 hours after hospital admission, there is still a need for development of earlier markers that can reliably rule out myocardial damage from the emergency room at patient presentation and, hopefully, detect myocardial ischemia also in the absence of irreversible myocyte injury (65). Fortunately, both industry and academia are relentlessly producing an intense research effort of finding new serum biomarkers that are released very early after the onset of myocardial ischemic damage. Under investigation are two main classes of indicators: markers of early injury/ischemia and markers of coronary plaque instability and disruption (*Table II*).

Table II Proposed biochemical markers for early detection of myocardial damage in blood

Markers of cardiac ischemia
- Creatine
- Unbound free fatty acids
- Glycogen phosphorylase isoenzyme BB
- Ischemia-modified albumin

Markers of plaque instability
- Soluble CD40 ligand
- Whole blood choline
- Monocyte chemoattractant protein-1
- Myeloperoxidase
- Pregnancy-associated plasma protein A

Markers of cardiac ischemia

Recent publications have explored the rationale for diagnosing myocardial ischemia in advance (or in absence) of the occurrence of irreversible damage (65, 66). As the explicit goal is maintain microcirculatory flow to prevent even minor infarctions, only a marker that precedes necrosis and permits to prevent its consequences can meet clinical needs (*Table III*) (66). A marker of cardiac ischemia could also be valuable in distinguishing acute MI from nonischemic causes of myocardial necrosis that lead to increases in cardiac troponins.

Table III Attributes of an ideal biochemical marker for cardiac ischemia[a]

- Detection of myocardial ischemia whether or not necrosis is present
- No elevation during ischemic injury of other organs
- Rapid rise and fall after ischemia
- Reliable preanalytical and analytical performance
- Simple to measure with a turnaround time of <60 minutes

[a] Modified from ref. 66.

Creatine is a nonprotein nitrogenous compound, present in mammalian muscles. It has a considerably lower molecular mass (131 Da) compared with conventional cardiac protein markers; release into the circulation may therefore occur at an early stage of myocardial damage, allowing rapid diagnosis (67). Release of creatine from skeletal muscle may however interfere with the interpretation of data. A recent study investigated the relationship between serum creatine and ECG indices of ischemia during cycloergometric exercise testing (68). Participants who met the ECG criteria for ischemia had higher serum creatine concentrations after exercise. Conversely, no relationship was found between total CK, CK-MB and myoglobin and the presence of ECG changes (68). The same authors reported however contradictory results by showing no significant changes in creatine concentrations of patients with unstable angina (69).

Previous studies have shown that accumulation in blood of free fatty acids unbound to albumin (FFAu) during acute myocardial hypoxia can have a deleterious effect on myocardial function by inducing arrhythmias through a detergent effect on the cell-membrane with cation loss and resultant development of ectopic pacemaker activity (70). More recently, the increase of FFAu with myocardial ischemia has been evaluated for early identification of cardiac injury (71). Two groups of investigators have preliminarily studied the sensitivity of this marker at patient presentation to the emergency room, showing FFAu elevations well before traditional markers of cardiac necrosis (72, 73). In particular, the sensitivity of FFAu at admission was >90% in both studies.

Glycogen phosphorylase isoenzyme BB (GP-BB) has been proposed in the middle of 1990s as a potential early marker of cardiac damage (74). The physiological role of this enzyme is to provide the fuel for the energy supply required for muscle contraction by mobilizing glycogen. It exists in the cardiomyocyte in association with glycogen and the sarcoplasmatic reticulum, forming a macromolecular complex. The degree of association of GP with this complex depends on the metabolic state of the muscle. With the onset of tissue hypoxia, when glycogen is broken down and disappears, GP becomes soluble and can move from the peri-sarcoplasmatic reticulum compartment directly into the extracellular fluid (75). In preliminary studies, GP-BB was significantly more sensitive than CK-MB and myoglobin for diagnosis of MI during the first 2 to 4 hours after the onset of chest pain (76). GP-BB is however not a heart-specific protein and thus its specificity for myocardial damage is limited. Furthermore, most of the published work has been produced based on one assay but that is not widely available.

The discovery that albumin in serum of patients with myocardial ischemia exhibited lower metal binding capacity for cobalt than the albumin in serum of normal subjects was originally made by Bar-Or et al. (77). Based on these observations, an assay was recently developed in which cobalt not sequestered at the N-terminus of albumin is detected using a colorimetric indicator (78). In sera of normal subjects, more cobalt is sequestered by albumin, leaving less cobalt to react with indicator. Conversely, in sera from patients with ischemia, less cobalt is bound by the ischemia-modified albumin (IMA), leaving more free cobalt to react with indicator. Significant changes in albumin cobalt binding have been documented to occur minutes after transient ischemia induced by balloon angioplasty and to return toward baseline within 12

hours (79, 80). However, increases in IMA could also be observed during ischemia related to injury of organs other than myocardium (81). In addition, a deletion defect of the N-terminus of albumin has recently been documented in a nonischemic individual that was responsible for reduced cobalt binding and, consequently, for false-positive test results (82). Thus, the specificity of the measurement of IMA for myocardial ischemia warrants additional investigation.

Markers of plaque instability

A growing understanding of the importance of the rupture of atherosclerotic plaque in the pathogenesis of coronary events has led to the identification of an expanding array of markers of plaque instability (83). Markers of platelet, monocyte/macrophage and polymorphonuclear neutrophil activation, matrix metalloproteinase secretion and endothelial cell dysfunction have been proposed.

CD40 ligand is a trimeric, transmembrane protein present in platelets and, together with its receptor CD40, is an important contributor to the inflammatory processes that lead to coronary thrombosis (84). After platelet stimulation, CD40 is rapidly translocated to their surface and then cleaved, generating a soluble fragment [soluble CD40 ligand (sCD40L)] having prothrombotic activity (85). Recent papers provided important information about the clinical relevance of sCD40L in ACS patients (86, 87). Elevation of sCD40L indicated an increased risk of cardiac events during six months of follow-up and identified subjects who are likely to benefit from antiplatelet treatment (86). More interestingly, in patients who were negative for myocardial necrosis, assessed by cardiac troponin, sCD40L seemed to identify a further subgroup at increased cardiac risk, suggesting that measurement of sCD40L may have additive benefits if combined with the current biochemical standard for MI (87). Results of these studies, however, require confirmation in unselected populations. As sCD40L is known to be elevated in individuals with a broad spectrum of inflammatory conditions, a question on marker specificity also arises (85).

Experimental studies have demonstrated that phospholipase D enzyme activation and consequent release of choline in blood are related to the major processes of coronary plaque destabilization (88). Based on these processes, increased blood concentrations of choline have to be anticipated after plaque disruption and myocardial ischemia in patients with ACS. In a recently study, choline detected troponin-negative patients with high-risk unstable angina with a sensitivity and specificity of 86% (89). Additional studies are however needed to fully investigate the clinical significance of this marker.

Monocyte chemoattractant protein-1 (MCP-1) is a chemokine responsible for the recruitment of monocytes to sites of inflammation that appears to play a critical role in the initiation of the fatty streak and promotion of plaque instability (90). In case-control studies, plasma MCP-1 concentrations were associated with restenosis after coronary angioplasty (91). However, in a prospective study on a large cohort of ACS patients, the distribution of MCP-1 values in the healthy subjects and the study population overlapped considerably, indicating that MCP-1 is probably not useful for diagnosing unstable ACS (92).

Myeloperoxidase (MPO) is a mediator enzyme secreted by a variety of inflammatory cells, including activated neutrophils and monocytes/macrophages, such as those found in atherosclerotic plaque (93). It possesses proinflammatory properties and may contribute directly to tissue injury (94). Two recent experiences evaluated MPO as predictor of cardiac risk in populations with different prevalence of ACS (95, 96). In both studies, a single measurement of plasma MPO at hospital admission predicted the risk of major adverse cardiac events in the ensuing 30-day and six-month periods. Even in the absence of myocardial necrosis, i.e. consistently negative cardiac troponin, baseline measurements of MPO significantly enhanced the identification of patients at risk (95, 96). Also, MPO predicted adverse outcome independent of sCD40L; in ACS patients with undetectable troponin concentrations and normal sCD40L levels, high MPO concentrations remained predictive for increased cardiac risk (96). This may imply that neutrophil activation represents an adjunct pathophysiological event in ACS that is distinctly different from platelet activation.

Pregnancy-associated plasma protein A (PAPP-A) is known as a high-molecular weight (200 kDa) glycoprotein synthesized by the syncytiotrophoblast and is typically measured during pregnancy for screening of Down syndrome. It was reported to be an insulin-like growth factor (IGF)-dependent IGF binding protein-4 specific metalloproteinase, being thus a potentially proatherosclerotic molecule (97). Bayes-Genis et al. (98) showed the presence of PAPP-A in unstable plaques from patients who died suddenly of cardiac causes and described increased PAPP-A concentrations in serum of patients with both unstable angina and acute MI. PAPP-A measurement appeared to be valuable for detecting unstable ACS even in patients without elevations of biomarkers of necrosis, such as cardiac troponins, thus potentially identifying high-risk patients whose unstable clinical situation might otherwise remain undiagnosed (99). Preliminary results provide evidence that circulating PAPP-A during ACS is different from PAPP-A isolated from pregnancy sera (100). Physiologically, PAPP-A circulates in a heterotetrameric complex consisting of two PAPP-A subunits covalently bound with two subunits of the proform of eosinophil major basic protein (proMBP), its endogenous inhibitor (101). PAPP-A found in unstable plaques is conversely present as a homodimer, thus making it difficult to measure PAPP-A by immunoas-

says which are designed to detect intact molecules (102). Also, the kinetics of PAPP-A release and the corresponding optimal sampling protocols in ACS remain to be determined (100).

Cardiac natriuretic peptides

The last part of this review is devoted to consider the role and the importance that biomarkers are assuming in the clinical assessment of cardiac function. This is an area where biochemical tests have traditionally not played any role. With the recent clinical characterization of CNP, this promises to be an emerging field of Laboratory Medicine.

Natriuretic hormones are a family of related peptides with similar peptide chains as well as degradation pathways. CNP include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), while other natriuretic peptides, such as C-type natriuretic peptide and urodilatin, are not produced and secreted by cardiac tissue but by other tissues (103).

ANP and BNP derive from precursors, the preprohormones, which contain a signal peptide sequence at the N-terminal end (104). In particular, BNP derives from a precursor, called preproBNP, which in humans contains 134 amino acids including a signal peptide of 26 amino acids. The proBNP containing 108 amino acids is produced by cleavage of the signal peptide, when appropriate signals for hormone release are given. ProBNP is further split into an inactive N-terminal fragment, the Nt-proBNP 1-76, and the 77-108 peptide, the BNP, which is considered to be the biologically active hormone (104).

Whereas ANP is secreted mainly from atrial cardiomyocytes, BNP is preferentially produced and secreted in the left ventricle, even if this may be a simplification, as the right side of the human heart also synthesizes and secretes BNP in response to disease (105). The precise mechanisms controlling production and secretion of CNP are still unclear, although ventricular stretch and wall tension are likely to be important (103). In general, the plasma concentrations of these peptides are increased in diseases characterized by an expanded fluid volume, such as renal failure, primary aldosteronism and CHF, or by stimulation of peptide production caused by ventricular hypertrophy or strain, thyroid disease, excessive circulating glucocorticoid or hypoxia (106). In agreement with a recent commentary (107), it is therefore surprising that researchers focused for so long on the single issue of whether CNP identified left ventricular (LV) systolic dysfunction or not, and did not recognize that these peptides should be used in a more general way in order to detect all cardiac abnormalities, including LV hypertrophy, LV diastolic dysfunction, atrial fibrillation and significant cardiac valve disease. It is now clear that measurement of CNP in plasma does not unequivocally diagnose the specific underlying cause of a myocardial dysfunction but rather verify the need of further cardiac examination. High concentrations of these markers call for further investigations: echocardiography is therefore required to identify the underlying cardiac pathology, revealing the systolic and diastolic ventricular function and thus determining the appropriate treatment. This was instrumental for the ESC to incorporate CNP in the first step for the evaluation of symptomatic patients suspected of CHF (13).

Although the reliable role of CNP in identification and management of patients with symptomatic and asymptomatic ventricular dysfunction remains to be fully clarified, the clinical usefulness of CNP (especially BNP and Nt-proBNP) in evaluation of patients with suspected heart failure, in prognostic stratification of patients with CHF, in detecting LV systolic or diastolic dysfunction and in differential diagnosis of dyspnoea has been confirmed even more recently (108). BNP and Nt-proBNP have also emerged as prognostic indicators of long-term mortality early after an acute coronary event. This association was observed across the spectrum of ACS, including patients with ST-elevation MI, NSTEMI and unstable angina, those with and without elevated cardiac troponins, and those with and without clinical evidence of heart failure (109, 110). However, more work remains to determine the optimal decision limits for clinical interpretation, as well as the specific therapeutic strategies of persistent CNP elevation in these patients.

Generally speaking, CNP have now proven their value in clinical cardiology. However, important issues related to their clinical use are still open (*Table IV*) (111). A working list could include: the need of standardization of CNP immunoassays and of better definition of their analytical performance, with regard to the antibody specificity, calibrator characterization and influence of preanalytical factors; more complete understanding of cardiac secretion, molecular heterogeneity and metabolism of CNP and knowledge of their biological variation; and, from the clinical point of view, definition of optimal decision limits and possible use in combination with other biochemical markers, clinical findings, or haemodynamic parameters. Finally, additional work is needed to identify therapies that

Table IV Focal issues for cardiac natriuretic peptides

– Better analytical validation of CNP immunoassays
– Assay standardization
– Understanding of CNP secretion, metabolism and clearance
– Information on the CNP biological variation
– Definition of decision limits for different clinical situations and establishment of possible multimarker strategies
– Identification of therapies reducing the risk associated with CNP elevations

CNP; cardiac natriuretic peptides.

may reduce the risk associated with increased CNP concentrations. Additional studies are also needed to analyze the clinical relevance of CNP in the patient follow-up, as well as their cost-effectiveness in different clinical settings.

Conclusions

Over the last 50 years, the contribution of Laboratory Medicine in the management of cardiac diseases has become increasingly sophisticated (8). In the 1950s, Karmen, Wroblewski and LaDue first reported that enzyme released from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of MI (112). The ensuing years witnessed progressive improvement in the cardiac-tissue specificity of biochemical markers and a corresponding enhancement in the clinical sensitivity and specificity of their use. There is now accumulating evidence that a multimarker strategy, employing a pathobiologically diverse set of biomarkers, is likely to add importantly in the assessment of patients with cardiac disease (113). In particular, markers of plaque destabilization and/or markers of myocardial ischemia could be added to the existing markers of cardiac necrosis and function in this paradigm if shown to contribute additional independent information (*Figure 1*).

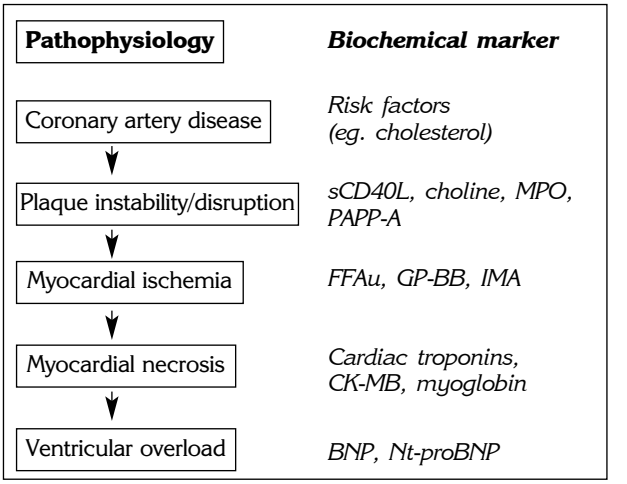

Figure 1. Pathophysiological interdependence of biochemical markers for the evaluation of cardiac disease:
SCD40L; soluble CD40 ligand, MPO; myeloperoxidase, PAPP-A; pregnancy-associated plasma protein A, FFAu; free fatty acids unbound to albumin, GP-BB; glycogen phosphorylase isoenzyme BB, IMA; ischemia-modified albumin, CK-MB; creatine kinase isoenzyme MB, BNP; B-type natriuretic peptide, Nt-proBNP; N-terminal fragment of proBNP

BIOHEMIJSKI MARKERI SRČANIH OBOLJENJA

Mauro Panteghini

Clinical Chemistry Laboratory 1, Spedali Civili University Hospital, Brescia, Italy

Kratak sadržaj: U radu se iznose najnovija saznanja o određivanju biohemijskih markera iz kliničke kardiologije i diskutuju neka značajna pitanja razvoja u ovoj oblasti. Biohemijski markeri imaju centralnu ulogu u dijagnostikovanju i praćenju pacijenata sa akutnim koronarnim sindromom, kao što se potvrđuje uvođenjem srčanih troponina u nove međunarodne preporuke za pacijente sa akutnim koronarnim sindromom i pri redefinisanju infarkta miokarda. Uprkos uspehu srčanih troponina, još uvek postoji potreba za razvijanjem ranih markera kojima se mogu isključiti akutni koronarni sindrom pri prezentaciji i detekciji miokardijalne ishemije a pri otsustvu ireverzibilnog oštećenja miocita. Trenutno se ispituju dve vrste indikatora: markeri ranog oštećenja/ishemije i markeri nestabilnosti koronarnog plaka i disrupcije. Takođe, karkaterizacijom srčanih natriuretskih peptida, laboratorijska medicina postaje sastavni deo protokola za praćenje i procenu srčane funkcije.

Ključne reči: biološki markeri, dijagnoza, infarkt miokarda, troponin

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