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Biochemical markers of cardiac damage: from efficiency to effectiveness

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Abstract

Testing for the diagnosis of acute myocardial infarction and other diseases included in the spectrum of the so-called "acute coronary syndrome" is rapidly changing from the traditional enzymatic assays to mass measurement of more specific and sensitive markers (cardiac troponins, CK-MB and myoglobin). Several questions have arisen since the introduction of these new markers into the clinical setting: the choice of strategies for optimizing the utilization of biochemical assays combining different (early and specific) markers, the rationale for sampling specimens and the identification of clinically useful turnaround times. The impressive clinical specificity and sensitivity assured by the measurement of cardiac troponins should be used for improving the effectiveness of patients' diagnosis and treatment. Troponins could be the paradigm of how a new diagnostic test and a therapeutic advance can be combined to the benefit of patients with acute coronary syndromes. In fact, in acute myocardial infarction (AMI) patients as well as in patients suffering from stable and unstable angina, the measurement of troponins alone, or combined to that of other biochemical markers, should be of practical value for the diagnosis, for the prognosis and for selecting the most effective therapeutic treatment. Limitations in cardiac markers should be classified into two groups: temporary and intrinsic limitations. Temporary limitations are: (a) current assays are not specific as to the analyte, (b) the limited standardization precludes a comparison between results obtained with different techniques. Intrinsic limitations are the elevation of troponins in the so-called "minor myocardial damage", which often cannot be confirmed by other techniques, the evidence that other heart diseases, such as congestive heart failure and myocarditis, can lead to an increase in troponin concentrations, and finally that troponin is not an early marker. A sound cooperation between cardiologists, physicians and laboratory specialists in explaining and understanding the advantages and limitations of current biochemical markers should allow us to move from efficiency to clinical effectiveness.

Keywords: Acute coronary syndrome; Turnaround time; Troponins; Standardization; Early markers; Clinical specificity; Clinical sensitivity

1. Introduction

Cardiovascular disease will continue to be a very important cause of mortality, morbidity, and rising costs far into this new century. In industrialized countries, we will continue to have a high incidence of cardiovascular disease for two main reasons: (1) more patients are kept alive during the acute phase of ischaemic heart disease, thus becoming patients with a chronic disease who often develop heart failure; and (2) ageing in the population will result in increasing numbers of patients with degenerative conditions, including some cardiovascular diseases.

In developing countries, "westernization" (e.g. smoking, changes in dietary habits, a more sedentary

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life-style, etc.) will increase the incidence of heart disease. The predictions for deaths from ischaemic heart disease at all ages in developing countries are appalling. In 1990, 1.8 million men and 1.7 million women in the developing world died from coronary disease. Those figures are likely to reach 4.3 million and 3.5 million, respectively, by the year 2020 [1].

This trend toward an increase in patients with chronic illnesses will create a very costly health problem. In fact, although we have seen formidable improvements in our diagnostic and therapeutic abilities, most of the treatment we give is only palliative.

This has prompted us to make a rigorous evaluation of the value and costs of tests and treatment, and to develop guidelines in an effort to achieve the most efficient care for acute coronary syndromes (ACS) patients. In an era of evidence-based coronary care, for example, the length of hospital stay being a major component of costs, Newby et al. [2] have published a paper in which they estimate the additional cost per year of life saved by prolonging hospitalization beyond day 3 for patients with uncomplicated MI. After comparing this price tag with other life-saving interventions for which there is general acceptance of the associated costs to society, they concluded that hospitalization beyond three days after thrombolysis is economically undesirable by conventional standards.

However, we will see in the next century and beyond that palliative treatment will gradually be replaced by curative treatment, eventually leading to a marked reduction in and then the disappearance of cardiovascular diseases through the use of preventive measures [3].

The evaluation of patients admitted to hospital with acute chest pain is time-consuming and expensive, and a substantial proportion of these patients do not really have an acute coronary syndrome (ACS). The primary aim of risk stratification, which is usually carried out in the Emergency Room, is to identify or rule out life-threatening conditions such as myocardial infarction or unstable angina. The unification of different pictures of coronary artery disease under the single term "acute coronary syndromes" reflects the understanding that these conditions are caused by a similar pathophysiology, characterized by erosion, fissuring, or rupture of a pre-existing plaque, leading to intravascular thrombosis and an impaired myocardial blood supply [4]. The presence or absence of mechanical obstruction by the plaque and its content, the amount and extent of associated thrombus formation, and the degree of collateral circulation, determine the outcome of patients, particularly if myocardial ischemia resolves completely or results in minor or major myocardial infarction. The common pathophysiology of different presentations of ACS logically requires a new approach to their diagnosis and treatment.

Over the past few years, laboratory research in the field of acute coronary syndromes has moved along two complementary lines: the search for improved specificity and sensitivity of biochemical markers. The identification and development of assays for the determination of cardiac troponins has been the most important innovation in the field of cardiovascular laboratory diagnostics in the last decade. Does this discovery, together with other insights on cardiac biochemical markers, represent a simple laboratory improvement or does it represent a breakthrough with a high clinical impact?

The definition of myocardial infarction and the related utilization of biochemical markers were strictly associated to the previous knowledge of the natural history of ACS as well as to the limited therapeutic armamentarium. Thrombolytic treatments as well as angioplasty, on the one hand, and a new generation of pharmacological agents on the other have dramatically changed the scenario. Indeed, the dilemma we have to solve is: what now is the role of laboratory testing in ACS, or rather, what are the ACS patients' needs regarding laboratory testing?

We know, for certain, that in all patients with chest pain suggesting evolving myocardial infarction of less than 12 h's duration and with persistent ST elevation, immediate reperfusion therapy is indicated [5]. Cardiac markers have no role in either the diagnosis, or in the therapeutic decision, for these patients. However, a baseline value can be useful for prognostic purposes, for evaluating the success of therapy and for clinical monitoring.

2. The ST-segment elevation group

In the Gusto IIa cTnT substudy, in-hospital mortality was only 5% in the 324 AMI-patients with a

normal cTnT on admission, while mortality was as high as 12% in the 176 AMI-patients who presented with an elevated cTnT value on admission. Also, the rate for cardiogenic shock and frequency of congestive heart failure were much higher in patients admitted for AMI who already had elevated cTnT levels [6]. The observed hazard persisted for up to 3 years of follow-up. In the Gusto-III-study, the 30-day mortality rate was 6.2% in patients who were cTnT-negative on admission versus 15.5% in cTnT-positive patients [7].

3. ACS patients without ST-segment elevation

The role of laboratory information is less clear and debated "on the other side of the moon": in patients with ACS without persistent ST-segment elevation, immediate thrombolytic treatment is not beneficial but, even in the presence of an atypical or negative ECG, the risk, the medical outcome and therapeutic decision in the individual patient may be quite different [8].

The contribution of biochemical markers to a better understanding of pathogenetic mechanisms underlying ACS is well recognized, while the use of the same markers is debated and varies in different institutions.

However, several studies have evaluated the use of cardiac troponins in patients with non-Q wave infarction or unstable angina (UA), and have demonstrated that there is an association between an elevated troponin value and the risk of coronary events. Among patients with UA and non Q-wave MI, there is an increased risk of death within 6 weeks in those with a troponin I level of 0.4 mg/l or higher (3.7%) and the risk continues to increase as the cTnI level increases [9]. The risk of death persists after adjustments have been made for other baseline characteristics that are independently predictive of mortality.

In patients with angina at rest, a substantial hazard has been demonstrated at different follow-up intervals. In the study by Ottani et al. [10], in the total cohort of patients studied, (overall) 10.7% had an adverse event within 30 days. The mortality rate was 2.7% and the MI rate was 8%. The frequency of the composite end-point of death and non-fatal MI was 27.7 for individuals with elevated cTnI levels and 17 for patients with elevated cTnT. The relative risk was 3.2 for patients with an increase in cTnI and 1.7 for patients with elevated cTnT levels.

More importantly, a treatment benefit was recorded in an increasing number of trials for troponin I and T-positive patients receiving the glycoprotein IIb/IIIa antagonist (e.g. abciximab and tirofiban) and the low-molecular weight heparin, dalteparin [11,12].

4. Troponins as a new paradigm

Thus, troponins are the paradigm for how a new diagnostic test and a therapeutic advance can be combined for the benefit of patients with acute coronary syndromes.

As yet, no other clinical information nor any other diagnostic tests can replace the information assured by the measurement of troponins, and probably this is a source of concern for cardiologists and clinicians: they have to believe in a biochemical marker. This state of affairs has led to two opposite (and erroneous) types of behavior: some clinicians have rejected the troponins because of their supposedly over-high sensitivity and the utilization of CK-MB measurement has even been proposed to counteract and decrease the disadvantages of the over-high sensitivity of troponins' assay. On the other hand, other clinicians have dismissed any clinical judgment for applying a troponin-centered vision to the management of patients. However, no laboratory test, even if it is highly sensitive and specific, can replace clinical reasoning, and this also applies to troponins. In fact, some reports have described cases of false-positive troponins underlying the limitation of the marker.

As stated by Bock [13] in a recent editorial, concerning troponins, we must ask ourselves how specific is specific. There are several limitations to the information assured by the measurement of troponins, and they are partly temporary and partly "intrinsic", and without any solution.

Temporary limitations: (a) current assays are not specific as to the analyte. In fact, some assays are subject to interference from rheumatoid factors, from circulating antibodies, from hemoglobin, bilirubin and other constituents [14,15]. (b) The limited stan-

dardization of troponin I assays precludes a comparison between results obtained with different techniques and, therefore, by different laboratories. Of course, these limitations are temporary and efforts are being made to overcome them. Regarding standardization, scientific organizations as well as manufacturers are striving to adopt standardized antibodies and calibrators. The "intrinsic" limitations of troponins are: (a) small elevations in troponins can be ascribed to "minor myocardial damage", an entity essentially defined by a small elevation in these cardiospecific markers. In some of these situations, clinicians cannot confirm the biochemical finding because of the current imperfect "gold standard"; (b) other heart diseases, such as congestive heart failure and myocarditis can lead to an increase in troponin concentrations in serum, and, in some cases, the levels have been shown to be correlated with disease severity; (c) despite its impressive specificity, troponin is not an early marker; its main drawback is therefore that, like CK-MB, it does not appear in the circulation until a few hours after myocardial infarction. However, a diagnostic strategy which combines the specificity of troponins with the sensitivity of the best early available marker, myoglobin, may overcome this supposed limitation [16]. There is, in fact, wide consensus on the utilization of two biochemical markers [17,18].

The question regarding the supposedly "over-elevated sensitivity" of troponins is related to our imperfect knowledge of how much necrosis is required to cause myocardial damage severe enough to be considered "infarction". In a pure physiologic sense, in fact, any detectable necrosis is acute myocardial infarction, as stated by Jesse [19] and, more convincingly, it becomes increasingly difficult to distinguish between outcomes in patients with minor AMIs and in those with "minor myocardial damage" due to unstable angina. Probably, less emphasis should now be given to the definition of "myocardial infarction" and we should identify and treat, with different therapeutic strategies, all ischemic myocardial injuries by translating into clinical practice the evidence of the continuum of ACS. In other words, the categorization of patients with ACS must not be an obstacle to any improvement in medical outcome that can be achieved through a more accurate diagnosis and an adequate treatment. The utilization of a very sensitive biochemical marker, should, moreover, allow us to adopt different clinical cut-offs so as to identify different degrees of myocardial damage requiring different therapeutic approaches. This cannot be done by adopting traditional markers, which are only sensitive enough to confirm massive transmural infarctions.

From a clinical viewpoint, currently the greatest limitation seems to be the evidence that troponins are cardiospecific, but not "ischemia or atherosclerosis-specific" [20]. Basically, this is a relative limitation and increasing interest is being shown in the measurement of troponins as a marker of myocardial damage occurring in myocarditis, congestive heart failure, stunning and chemotherapy. Fortunately, the kinetics of the marker can help in differentiating between this type of damage and that occurring in evolving ischemic diseases, and this reaffirms the difference between morphology as well as imaging techniques and biochemical testing, the latter being more adequate for the monitoring of disease evolution through serial measurements. In practical terms, this means that clinical reasoning should be based at least on two serial measurements of biochemical markers, mainly when clinical symptoms and other diagnostic information (ECG) are equivocal.

5. Search for early markers

The other field of study is the search for early markers. The state-of-the-art is that among the commercially available markers, myoglobin is the earliest indicator. Other recent advances have been the discovery of glycogen phosphorylase BB, for which no real-time assay is available, and new insights on the early expression of HIF and VEGF [21].

Therefore, in patients with chest pain and equivocal ECG patterns, the adoption of a diagnostic strategy which combines the sensitivity of myoglobin, which has a high negative predictive value, with the specificity of troponins allows cardiologists to efficiently and effectively diagnose and treat most ACS patients [22 23]. Other "early" indicators are markers of plaque rupture (e.g. markers of pro-coagulant activity such as Thrombus Precursor Protein and D dimer) and markers of inflammation, C reactive protein (CRP) in particular.

An increasing body of evidence indicates that CRP is a potent predictor of risk, irrespective of other clinical and biochemical markers. We must adopt the new biochemical markers in clinical practice in order to improve upon medical outcome, and this calls for a sound cooperation in explaining and understanding the limitations and the advantages of these biochemical tools in the clinical setting. Finally, because in this field "time is life", there should be no further delay before introducing the new diagnostic strategy into clinical practice.

References

[1] Horton R. Future of European cardiology: continentally isolated or globally integrated? Lancet 1999;354:791–3.
[2] Newby LK, Eisestein EL, Califf RM, et al. Cost effectiveness of early discharge after uncomplicated acute myocardial infarction. N Engl J Med 2000;342:749–55.
[3] Simoons MS, Boersma E, van der Zwaan C, Deckers JW. The challenge of acute coronary syndromes. Lancet 1999; 353(suppl. II):1–4.
[4] Braunwald E. Unstable angina: an etiologic approach to management. Circulation 1988;98:2219–22.
[5] Fibrinolytic Therapy Trialists' (FTT) Collaborative Group, Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311–22.
[6] Ohman EM, Armstrong PW, Christenson RH, et al. For the GUSTO IIa investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996;335:1333–41.
[7] Ohman EM. Gusto III symposium. XIXth Congress of the European Society of Cardiology, Stockholm 1997.
[8] Klootwijk P, Hamm C. Acute coronary syndromes: diagnosis. Lancet 1999;353(suppl. II):10–5.
[9] Antman EM, Grudzien C, Mitchell RN, Sacks DB. Detection of unsuspected myocardial necrosis by rapid bedside assay for cardiac troponin T. Am Heart J 1997;133:596–8.
[10] Ottani F, Galvani M, Ferrini D, et al. Direct comparison of early elevations of cardiac troponin T and I in patients with clinical unstable angina. Am Heart J 1999;137:284–91.
[11] Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponoin T levels. N Engl J Med 1999; 340:1623–9.
[12] Heeshen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. Lancet 1999;354:1757–62.
[13] Bock JL. Cardiac troponin: how specific is specific? Am J Clin Pathol 1999;112:739–41.
[14] Dasgupta A, Banerjee S, Datta P. False-positive troponin I in the MEIA due to the presence of rheumatoid factors in serum. Am J Clin Pathol 1999;112:753–6.
[15] Ver Elst KM, Chapelle JP, Boland P, Demolder JSC, Gorus FK. Analytic and clinical evaluation of the Abbott AxSYM cardiac troponin I assay. Am J Clin Pathol 1999;112:745–52.
[16] Zaninotto M, Altinier S, Lachin M, Celegon L, Plebani M. Strategies for the early diagnosis of acute myocardial infarction using biochemical markers. Am J Clin Pathol 1999;111: 399–405.
[17] Wu AH, Apple FS, Gibler B, Jesse R, Warshaw M, Valdes R. National Academy of Clinical Biochemistry-Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999;45: 104–21.
[18] Panteghini M, Apple FS, Christenson RH, Dati F, Mair J, Wu AH. Use of biochemical markers in acute coronary syndromes. IFCC Scientific Division, Committee on Standardization of Markers of Cardiac Damage. Clin Chem Lab Med 1999;37:687–93.
[19] Jesse RL. Myocardial necrosis in "pure unstable angina": identification of high-risk subgroups or a contradiction in terms? Am Heart J 1999;137:190–2.
[20] Jaffe AS. Pandora's box is torn asunder. Am Heart J 1999; 138:9–12.
[21] Lee SH, Wolf PL, Escudero R, et al. Early expression of angiogenesis factor in acute myocardial infarction. N Engl J Med 2000;342:626–33.
[22] Plebani M, Zaninotto M. Diagnostic strategies in myocardial infarction using myoglobin measurement. Eur Heart J 1998; 19(Suppl. N):N12–5.
[23] Plebani M, Zaninotto M. Cardiac markers: centralized or decentralized testing? Clin Chem Lab Med 1999;37:1113–7.