BIOCHEMICAL ADVANCES IN DETECTION OF THE ACUTE CORONARY SYNDROMES : IMPLICATIONS FOR THERAPEUTIC DECISIONS

J.H. Keffer.

Department of Laboratory Medicine and Pathobiology, University of Toronto
and Spectral Diagnostics Inc., Toronto, Canada.

ABSTRACT

In this paper, I have attempted to place the evolving insights of the pathophysiology of coronary atherosclerosis in the context of the conventional perspective of clinical medicine. We strive to prevent death and to relieve suffering. Our clinical tools are critical but limited. Troponin, a biomarker of unprecedented organ specificity, in the context of the appropriate setting of new chest pain (or its equivalent syndrome), is an extraordinary aid to clinical diagnosis. Highly effective therapy is evolving which reduces loss of myocardium, undoubtedly reducing not only acute death but progression to congestive heart failure. Even if the newer therapies of the GpIIb/IIIa platelet antagonists and anti-thrombins are not yet widely employed, or may not be available to some physicians, the convincing demonstration of myocardial injury by troponin presents objective evidence to both the patient and the attending physician that serious compliance with a program of risk reduction must be urgently considered. Hoeg has described the mosaic of risk factors beyond the conventional and often ignored basic ones (JAMA, 1997, 277, 1387-1390). He provides thoughtful hope and encouragement for both patient and physician to do more in prevention of the subsequent predictable progression. We should look on a troponin positive vague unstable angina event as similar to a tremor which precedes a subsequent earthquake. Although the mass of myocardium lost in such an episode may be small, it is a warning of the major acute myocardial infarction which can be predicted to follow at a later time if the course of the individual patient is not altered. Troponin is the objective evidence.

INTRODUCTION

Progress in the development of improved analytical procedures for the detection of markers of myocardial injury (1) have paralleled

progress in the understanding of the underlying pathophysiology (2,3) of ischemic coronary artery disease. We are now poised for the era of successful treatment beyond thrombolysis of the patient presenting with Q-wave Acute Myocardial Infarction (AMI). We can more effectively treat the high risk Unstable Angina (UA) patient as well as the non-Q-wave AMI. The key to the successful application of these

---

Author for correspondence :

Dr. J.H. Keffer, M.D. Professor, Chief Medical
Officer & Vice President, Spectral Diagnostics
Inc., 135-2 The West Mall, Toronto, Ontario,
M9C 1C2 Canada

E.mail : kef@spectraldiagnostics.com

Fax : 416 - 626 - 2739

advances is the reliable and confident documentation of the fundamental process of plaque rupture followed by sufficient impairment of physiologic function producing myocyte injury. This is manifest by the appearance of troponin in the blood of an appropriate candidate patient.

The New Troponin Rationale

If one considers the following six related points, the critical role of troponin to modern clinical medicine will be sustained.

1. Coronary artery disease is highly prevalent.
2. The diagnosis of the related acute coronary syndromes is difficult.
3. The pathophysiology is well-defined.
4. Troponin definitively rules in or rules out "AMI".
5. Troponin further defines "high risk" UA.
6. Troponin supports selection of candidates for therapy.

In this paper, I shall discuss each of these points. The first five are generally acknowledged, the final one is now coming to light and already supported by strong data.

Coronary artery disease is the leading cause of death in the United States and although progress has decreased fatality of AMI, the number of cases continues to rise (4). Estimates of chest pain presentations for emergency evaluation range from 5 to 10 million per year. Throughout the world, this is a highly significant disease.

The classic presentation of the AMI involves sudden onset of severe pre-cordial chest pain, radiation to the neck or arm and diaphoresis.

While this is common, it occurs in fewer than 50% of AMI cases. In such cases, no physician requires a laboratory test, or for that matter, an electrocardiogram (ECG) to know that the patient is at risk and requires further evaluation including hospitalization. These cases comprise fewer than 10% of the cases presenting to the emergency department for evaluation. Distributed throughout the remaining 90% are presentations ranging from some variety of chest pain to those simulating biliary stones, or even simply a sense of weakness (5). It is for this reason that we continue to see reports of missed AMI in the 2-5% range, and high medical malpractice payments in the United States. Well documented studies confirm the difficulty of diagnosing this entity. As such, standardized protocols are advocated for the purpose of successfully documenting the absence as well as the presence of AMI (6,7).

Progress over several decades has confirmed that in the vast majority of patients experiencing AMI, atherosclerotic plaque rupture followed by localized platelet activation, with thrombin activation leads to localized clot formation with impedance of blood flow. In turn, this leads to impaired oxygenation, nutrient supply and removal of waste metabolites. Cardiac myocytes are injured or killed. Thrombolysis ensues endogenously and may be aided by therapeutic enhancement leading to successful or unsuccessful re-establishment of the flow. There may be microaggregates of platelet thrombi downstream leading to microinfarction of the distal vascular bed. Clinically, the imperfect correlates of these processes are the spectrum of UA to Q-wave AMI, with a common shared process of plaque rupture and activation of

clotting. If studied immediately by angiography (8), UA will infrequently, but occasionally, have complete occlusion while Q-wave AMI will be demonstrably occluded in more than 85% of cases providing the reason why thrombolysis is potentially harmful for UA, lacking an occlusion to attack, while the new thrombus of Q-wave AMI is the appropriate target for this form of therapy. Currently, extending our understanding to the molecular level, there is intense interest in the inflammatory cellular activities leading to plaque destabilization. These appear to relate to oxidized lipoprotein activation of macrophages resident within the lesions causing cellular release of cytokines and metallo-proteinases, collagenases and other agents which breakdown the collagen barrier between the lipid pool of the atheroma and the lumen of the artery. This predisposes the lesion to rupture (2). Much is known with regard to reducing the risk factors associated with these processes and this elevates the priority of recognizing the individual at risk (9). While studies of inflammatory markers of these underlying processes are of interest, to date, they are non-specific. This makes the recognition of troponin in the chest pain patient as more important than simply the confirmation of AMI.

Troponin, as a test for confirmation of AMI is now acknowledged to be the definitive test (1,7). It is a new "Gold Standard" and has replaced the CKMB assay. The latter is well-known and documented to lack cardiospecificity with non-cardiac elevations due to skeletal muscle disease, thyroid and renal disease and even labor and delivery. By contrast, cardiac troponin I has not been identified, to date, in any tissue other than the cardiac muscle cell. This is unique among diagnostic tests for any disease. Further,

not only is the marker specific but it is sensitive. It is now recognized that the troponin test, appropriately sampled over the time related to a clinical episode, correctly proves the absence of infarction in relation to that symptom or episode. Plainly spoken, if a patient presents with chest pain or "chest-pain equivalence", and if the symptoms are transient and not recurrent, the serial sampling for a maximum of 6-9 hours with absence of detectable troponin in the serum excludes the prior episode from being an infarct. That is not to say that the patient does not have symptomatic and significant ischemic coronary artery disease, however, infarction is excluded. This is true for CKMB as revealed in an excellent study by Robert's group (10) in which electron microscopic criteria were employed to study the correlation between necrosis and CKMB. Their conclusion is that the appearance of the serum protein markers always was associated with demonstrable changes of necrosis, and conversely, if the marker did not appear in the serum, then no EM changes of necrosis could be identified. While troponin was not studied, we can conclude from risk stratification clinical studies that troponin is more sensitive to ischemia than is CKMB and thus the absence of troponin absolutely excludes infarction.

That troponin testing defines a group of patients beyond those conventionally diagnosable as AMI has led to special focus on the group of patients with UA who are troponin positive. Braunwald has long defined the distinction between Non-Q-AMI and UA as the presence of diagnostic CKMB in the former group and, implicitly, the absence of CKMB in UA (11). He extended this to include troponin positive, and CKMB negative UA patients in a recent lecture

(12). Referring to the chest pain emergency patient, he said: "Within that group (UA), there are patients who have an elevated troponin and who have no elevation of troponin. And it is the patients with the elevated troponin that many people refer to as "Minor Myocardial Injury" which is of tremendous importance from a prognostic point of view". He went on to emphasize: "It isn't the amount of myocardium that is damaged which is deleterious to the patients outlook, it is the fact that they have an active plaque which is shedding thrombi or atheromatous material causing microemboli and microinfarctions which elevates them as patients at risk". Indeed, Braunwald was referring to the twenty or more studies of troponin T and I which have shown independent risk stratification of patients with chest pain. A recent meta-analysis has been published summarizing the strong evidence in support of this concept (13). Thus, we must extend our diagnostic case-finding to identify this group as candidates for interdiction of the common underlying pathophysiologic processes unleashed by destabilized atherosclerotic plaque. We should recall that there are no patients with a unifocal plaque. It is always an extensive process when it becomes clinically detectable. The process of destabilization involves many plaques.

The final issue is that troponin positivity identifies the chest pain patient who is a candidate for the novel, yet expensive and potentially harmful newer therapeutic agents for the ACS. I refer to the new GpIIb/IIIa platelet antagonists and the low molecular weight heparins. While the scope of these revolutionary therapies is beyond this presentation, it is clear that both have merit and share the common

feature of substantial cost and some degree of potential side effects. As always, diagnosis should ideally select patients for rational therapy. There is already substantial evidence to support the use of troponin positivity for this purpose. The basis for this is the previously cited evidence that troponin is a sensitive marker for cardiac injury in a patient population with vague to non-specific symptoms in whom the ECG is recognized to be inadequate. The very cardiospecificity makes troponin an objective testimonial that cardiac disease is present. In the "CAPTURE" trial of abciximab, a platelet antagonist was evaluated in high risk chest pain patients awaiting balloon angioplasty. The treated group had a striking reduction of progression to infarction and dramatic reduction of peri-procedural infarction as contrasted with the placebo arm of the study. Notably, when the groups were sorted out by the presence or absence of troponin, there was no significant progression to AMI by the troponin negative group, therefore no significant reduction could be measurable if given the drug. By contrast, the progression to infarction was almost entirely in the troponin positive group and this was blocked by the drug (14). Similarly, significant discrimination of therapeutic benefit is made possible by troponin testing in the trials of the low molecular weight heparins, as already reported (15) and an array of other reports are in progress at the present time. All corroborate the same conclusion that the troponin positive chest pain patient is the appropriate candidate for greater therapeutic efforts and for urgent time-critical diagnosis to enable critical therapeutic decision. For this purpose, proven bedside rapid testing is desirable (16, 17).

REFERENCES

1. Keffer, J.H. (1996) Myocardial Markers of Injury. Evolution and insights. *Am. J. Clin. Path.* 105, 305-320.
2. Libby, P (1995) Molecular basis of the acute coronary syndromes. *Circulation* 91, 2844-2850.
3. Fuster, V. (1995) Elucidation of the role of plaque instability and plaque rupture in acute coronary events. *Am. J. Cardiol.* 76, 24c-33c.
4. Chesebro, J.H and Badimon, J.J. (1998) Platelet Glycoprotein IIb/IIIa Receptor Blockade in Unstable Coronary Disease. Editorial, *New Engl. J. Med.* 338, 1539-1541.
5. Hofgren, C., Karlson, B.W. and Herlitz, J. (1995) Prodromal Symptoms in subsets of patients hospitalized for suspected acute myocardial infarction. *Heart Lung* 24, 3-10.
6. Gibler, B., Runyon, J.P., Levy, R.C. (1995). A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann. Emerg. Med.* 25, 1-8.
7. Keffer, J.H. (1997) The Cardiac Profile and Proposed Practice Guideline for Acute Ischemic Heart Disease. *Am. J. Clin. Path.* 107, 398-409.
8. White, H.D. (1997) Unmet therapeutic needs in the management of acute ischemia. *Am. J. Cardiol.* 80(4a), 2B-10B.
9. Hoeg, J.M. (1997) Evaluating coronary heart disease risk. Presented for Grand Rounds at the Clinical Center of the National Institutes of Health. *J. Am. Med. Assoc.* 277, 1387-1390.
10. Ishikawa, Y., Saffitz, J.E., Mealman, T.L., Grace, A.M. and Roberts, R. (1997) Reversible myocardial ischemic injury is not associated with increased creatine kinase activity in plasma. *Clin. Chem.* 43, 467-475.
11. Antman, E.M., Tanasijevic, M.J., Thompson, B., Schactmann, M., McCabe, C.H., Cannon, C.P., Fischer, G.A., Fung, A.Y., Thompson, C., Wybenga, D. and Braunwald, E. (1996) Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *New Engl. J. Med.* 335, 1342-1349.
12. Braunwald, E. (1998) Plenary Session Lecture, American Association for Clinical Chemistry Convention, Chicago, USA. August 5, 1998.
13. Olatidoye, A.G., Wu, A.H., Feng, Y. and Waters, D. (1998) Prognostic Role of Troponin T versus Troponin I in Unstable Angina Pectoris for Cardiac Events with Meta-analysis comparing Published Studies. *Am. J. Cardiol.* 81, 1405-1410.

14. Hamm.C.W. (1998) Progress in the diagnosis of Unstable Angina and perspectives for treatment. Eur. Ht. J. 19 (Suppl N), N48-50.
15. Lindahl, B., Venge, P. and Wallentin, L. (1997) Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. J.Am.Clin.Chem. 29, 43-48.
16. Hamm, C.W., Goldmann, B.U., Heeschen, C., Kregmann, G., Berger, J. and Meinertz, T. (1997) Emergency room triage of patients with acute chest pain based on rapid testing for troponin T or I. New Engl.J.Med. 337, 1648-1653.
17. Heeschen. C., Goldmann, B.U., Moeller, R.H. and Hamm, C.W. (1998) Analytical performance and clinical application of a new rapid bedside assay for the detection of serum cardiac troponin I. Clin. Chem. 44, 1925-1930.