Troponin, delta change and the evolution of cardiac biomarkers – back to the future (again).

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Words 1897

Figures 0

References 48

Background

The diagnosis of myocardial infarction (MI) was originally considered fatal. It was not until Thomas Herrick demonstrated in 1912 that angina and myocardial infarction were separate clinical entities and not fatal (1) that the concept of cardiovascular diagnosis was launched. The first diagnostic test was the electrocardiogram (ECG) (2). This was followed by interest in the use of markers of inflammation, indirect by measurement of the white cell count and direct with measurement of C reactive protein (CRP). The first of the “traditional” cardiac enzymes was aspartate transaminase, first described by Arthur Karmen in 1954, followed by lactate dehydrogenase (LD) and its isoenzymes, hydroxybutyrate activity (as a surrogate for LD isoenzyme 1) and creatine kinase (CK) and its isoenzymes (3). The use of cardiac enzyme measurements, especially measurement of CK and its more cardiac specific MB isoenzyme, CK-MB was incorporated into the definition of myocardial infarction agreed by the World Health Organisation (WHO) (4).

3.1 Acute Myocardial Infarction The clinical diagnosis of acute myocardial infarction

is usually based on the history, the ECG, and serum enzymes.

A. History. The history is typical if severe and prolonged chest pain is present. Sometimes the history is atypical and the pain may be mild or even absent or other symptoms may predominate.

B. ECG. Unequivocal changes in ECG are the development of abnormal, persistent Q or QS waves,

and evolving injury current lasting longer than 1 day. When the ECG shows these unequivocal changes, the diagnosis may be made on the ECG alone. In other cases, the ECG may show equivocal changes, consisting of a) a stationary injury current, b) a symmetrical inversion of the T wave, c) a pathological Q wave in a single ECG record, or d) conduction disturbances.

C. Serum Enzymes. a) Unequivocal change consists of serial change, or initial rise and subsequent fall of the serum level. The change must be properly related to the particular enzyme and to the delay time between onset of symptoms and blood sampling. Elevation of cardiospecific isoenzymes is also considered unequivocal change.

The key features at this point are the primacy of the ECG and the use of term “unequivocal change”. Unequivocal change has been subsequently interpreted as decision limits twice the upper limit of normal (5). A value at or exceeding twice the upper reference limit (3.92 SD) corresponds to a probability that the result obtained is normal of 0.0044% and a probability of abnormality of 99.9956%.

The traditional approach was daily measurement of CK, AST and HBD or LD with a sequential rise and fall of the three markers over 3 days used to confirm the clinical diagnosis of MI. The cardiac enzyme panel was cheap and the timeframe matched the clinical care in use at the time (bed rest followed by slow mobilisation). More rapid diagnosis was possible by the use of serial measurement of the earliest rising markers, CK and CK-MB( 6). The need for a more rapid diagnosis to rule out myocardial infarction was recognised more in the United States where missed MI was a significant cause of Emergency Department (ED) malpractice claims (as the US had at that time 5 % of the world’s population but 50% of the worlds lawyers). Serial measurement over 6-8 hours allowed safe rule out and discharge (7). The only significant changes at this point were the development of immunoassay methods for CK-MB (8) and the evolutionary cul-de-sac of CK isoforms (9). Interest in more rapid diagnosis was revived by the advent of active management of myocardial infarction with thrombolytic therapy and anti-platelet agents as well as primary angioplasty.

The troponin paradigm

Immunoassay for cardiac specific proteins was developed initially in the late 1980’s heralded as part of the transformation of medicine by molecular biology (which is now starting to occur). The first documented test was for cardiac troponin I (cTnI) described by Cummins (10) in 1987 followed by the description in 1989 by Hugo Katus of the troponin T immunoassay (11). Whereas cTnT was patented by Boheringer-Mannheim cTnI was freely available. The first commercially successful immunoassay for cTnI was the Dade assay on a stat immunoassay platform (12), followed by other manufacturers producing assays of variable performance. The Boehringer assay was on a batch immunoassay platform (a considerable throughput disadvantage). At this point there was intense competition to introduce this new (and expensive) assay into routine clinical practice and obtain market share. The era of the “troponin wars” began with marketing claim and counterclaim (often not science based) of the “my assay is better than yours” and especially “cTnT is better than cTnI” and vice versa. This has resulted in some of the myths that are still with us and laid the foundations of the current clinician confusion,

There were two problems at this point. First, how to convince clinicians that this new test should replace their existing tests. Second, how to replace a set of tests that cost pence (or cents) with a test costing £20-30 (or euros). Sadly, we are not all regularly confronted with the scenario of the finance department ringing the laboratory head to urge them to spend more money. There were a number of factors that led to the adoption of cTnT and cTnI measurement. First was the demonstration that, in patients with unstable angina as adjudicated by current tests, cTnT (13) or cTnI (14) could be detected. This elevated cTnT or cTnI predicted a significant risk of the major adverse cardiac events (MACE) of death, subsequent myocardial infarction, readmission with a further episode of unstable angina or need for urgent revascularisation. Measurement of cTnT and cTnI were therefore diagnostically superior when assessed against independent outcomes, Second was the demonstration that in patients with unstable angina, an elevated cTnT or cTnI predicted a favourable response to intervention with antithrombotic (15) or antiplatelet medications (16) and revascularisation (17). Third, diagnosis of myocardial infarction was at that point using cardiac enzymes twice the upper reference limit. It was therefore possible to define a decision limit for cTnT and cTnI that conferred excellent sensitivity and specificity for the diagnosis of MI. This was not surprising as the “Gold standard” used was an inferior, less sensitive and much less specific test. The relative insensitivity of early assays meant troponin was undetectable in “normals”. The ED physicians and cardiologists now had a test that supported the binary diagnosis MI/no MI, simplifying clinical decision making (and some would say the death of clinical patient assessment). Finally, a single measurement 10-12 hours from admission was all that was required, allowing earlier discharge, hence improving patient flow. The troponin era was born.

The diagnostic and prognostic superiority of cTnT and cTnI led to the discussion initially at the AACC (5) and then within the ESC for the redefinition of MI with troponin as preferred biomarker (18). The key events from the laboratory perspective were the shift to the 99th percentile of cTn and the proposed imprecision goal of a CV of 10% or better at the 99th percentile. This was not met by any of the assays available at the time and led to manufacturers developing progressively more sensitive assays culminating in high sensitivity assay development.

Assay evolution and the development of high sensitivity assays.

There has been progressive improvement in assay performance with each new generation of troponin assay released (19). Improved assay performance may improve analytical specificity, such as reduced cross reactivity, but newer assays may produce different results from existing assays due to detection of different forms of cardiac troponin (20). Improved assay performance may reduce the number of analytical false positives (outliers) although these still occur (21) and need to be investigated as they may have causes such as reagent pack size and frequency of test utilisation (22). However, old problems, such as carryover, may still remain (23) and new problems, such as assay interference from biotin (24) appear.

The shift in diagnostic classification from an insensitive to a sensitive test, the use of the 99th percentile (a diagnostic discriminant that utilises a 1% probability of normality in an elevated value compared to a 0.0044% probability) and improvement in assay sensitivity resulted in the detection of troponin elevation outside the ACS population. This was, in fact, not a new finding (25) and had been shown in the original assays (12) (where choice of cut off ensured specificity). At the same time it resulted in the detection (and treatment) of more patients with ischaemic myocardial injury (26).

These shifts produced an existential crisis in both ED physicians and cardiologists with discussions of “troponinitis” and suggestions that less sensitive assays should be used, However, the consistent demonstration that troponin elevation (whatever the cause) was associated with an adverse prognosis means that a more nuanced approach is possible. The challenge is to distinguish between acute myocardial injury due to treatable conditions (most commonly acute plaque rupture/erosion with thrombosis) and acute myocardial injury secondary to other causes where ischaemic may or may not be a contributory factor and treatment of the underlying condition is required (27). These secondary injury cases are, paradoxically, more common that primary acute myocardial injury (28). High sensitivity troponin also allows identification of previously unsuspected myocardial injury in novel patient groups ranging from perioperative monitoring (29) to anthracycline toxicity (30). Improvement in assay sensitivity also suggests that the use of additional markers such as heart fatty acid binding protein and co-peptin (31) used to improve sensitivity in the early period following MI may not be required (32).

The advent of high sensitivity assays capable of measuring low levels of troponin with good precision has resulted in evaluation of a range of strategies for rapid diagnosis (33) including single measurement on admission (34;35) and short interval serial (1-2 hour) measurement strategies (36;37). Such strategies may be difficult to realise in routine clinical practice and short sampling intervals using low level cut offs, the 99th percentile and a delta value may be more appropriate (38). The importance of delta values cannot be overstated. Delta change for rapid diagnosis has previously been applied for rapid diagnosis where analytes have a wide reference interval (39;40). The biological variation of troponin is modest compared to the reference interval with a low index of individuality (41) even in chronic conditions such as renal failure where troponin is elevated (42;43). Hence use of a delta value will significantly improve diagnostic sensitivity, especially for rule out MI. There is a caveat here however. The delta values produced in research papers do not come from routine clinical use but from well controlled batch analysis on a single instrument. It has been suggested that at low troponin levels in routine clinical use, such levels of imprecision may not be achievable (44) a problem compounded when multiple analysers are used (45). Although rapid rule out has been proposed in ESC guidelines (46), the strategy is based on observational studies and not randomised clinical trials. From the laboratory perspective, very short analytical turnarounds are required, ideally suited to point of care testing (POCT) instruments. To date, no POCT method meet the analytical goals required to use these protocols.

The new frontier of troponin measurements will be in the management of chronic disease. There is convincing evidence that troponin measurement in the apparently healthy population correlates with underlying health status (47), outcome and response to statin treatment (48). The challenge will be to convert this into clinical management pathways.

Competing interests and other declarations None

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